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Some Considerations of the Roentgen Diagnosis of Silicosis and Conditions That May Simulate It[1]

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A FLUOROSCOPIC and roentgenographic examination of the chest, properly done, is the most precise method at our command for demonstrating the dynamics and visible shadows of pathological changes produced by pneumoconiosis or silicosis in the living individual. There are, however, many other conditions that produce shadows in the roentgenogram which may simulate some of those seen in pneumoconiosis. In spite of the fact that many excellent articles have been published on the various pneumoconioses, too many physicians, oftentimes radiologists, are making diagnoses of silicosis on insufficient data, merely because there is an abnormal shadow pattern and a history of employment in a dusty atmosphere.

In order to evaluate correctly the various shadows observed in a roentgen study of the chest, it is necessary to possess certain knowledge and experience both as regards the examination and the patient. Some of the more important requirements may be enumerated as follows:

1. A knowledge of the anatomy of the chest and some of the physiological manifestations of the various structures contained therein; an understanding of the histology of the lungs and of their lymphatic system.

2. A thorough familiarity with roentgenoscopic and roentgenographic appearances of the normal structures of the chest and their permissible variations (42).

3. A clear perception of the pathology of pneumoconiosis and of lesions that give a somewhat similar roentgenographic appearance.

4. Some knowledge of the history of the individual, especially his occupational record, and familiarity with the physical signs in the particular patient.

5. Some information concerning the industrial process that is responsible for the production of the dust involved. Dust counts at breathing levels and chemical analyses of the dust are exceedingly important when available.

With all of the above information, one should be able to render a diagnosis which, although presumptive, is likely to be correct in the majority of instances. Very often, however, an opinion is advanced on insufficient data, with the result that referring physicians become confused and injustices occur.

We have always regarded the roentgen examination as a consultation, and as such it is likely to be more valuable. An ideal program for the diagnosis of pneumoconiosis in the living would include a study by a

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group, the members of which would be a general physician, a rhinologist, a bronchologist, a clinical pathologist, a specialist in tuberculosis, a physiologist interested in the heart and lungs, an engineer, expert in industrial hygiene, and a general roentgenologist. Such a program is, of course, too ambitious for practical purposes, and in the majority of instances the physician tells the patient that he has pneumoconiosis or silicosis on the basis of a history of dust exposure, a physical examination which is thought to exclude other conditions that might produce similar symptoms, and the presence of abnormal shadows in roentgenograms of the chest which are compatible with those known to be present in pneumoconiosis. The fact that diagnoses are made in this manner places a tremendous responsibility on the roentgenologist, for he must not only describe the roentgen appearances, but after he has done so he must correlate the other information with which he has been supplied with his own observations, and arrive at a tentative or presumptive diagnosis. This is a safe procedure if, as radiologists, we fulfill our obligations to the referring physician and patient.

PNEUMOCONIOSIS

Pneumoconiosis is a broad generic term used to describe all forms of pulmonary reaction to dust lodging within the lungs, with no implication as to character, severity, or effect on function. Certain of these reactions may be demonstrated by roentgen examination of the chest, but in most instances they are entirely nonspecific, are unaccompanied by formation of progressive fibrosis, and are of no clinical significance. In the light of present knowledge, however, we recognize at least two clinically important specific pneumoconioses, namely, silicosis and asbestosis, as well as a number of benign pneumoconioses resulting from the inhalation of a variety of inert but radiopaque dusts. The former may be productive of disability, whereas the latter are of clinical significance only because they may lead to errors in diagnosis through their ability to produce upon the roentgenogram a nodular pattern at times indistinguishable from that occurring in silicosis.

THE SPECIFIC PNEUMOCONIOSES

Silicosis and asbestosis result from the inhalation of dust; both are capable of producing a progressive pulmonary fibrosis, and each condition produces a characteristic though radically different shadow pattern upon the roentgenogram. Here, however, their similarity ends.

Silicosis

Silicosis is thought to be due to the specific action of chemically free silicon dioxide in finely divided form, on the lung tissue. Clinical symptoms described as "phthisis" were associated with certain of the "dusty trades" in very early medical writings (1, 48), and even as early as the time of Pliny (47) efforts were made to curtail the inhalation of dust. Despite this interest in the subject, continued through the centuries, it was not until 1902 that dust inhalation *per se* was identified as the causative factor by Haldane, Martin, and Thomas (28). In their report on the health of Cornish miners, they stated that the primary injury to the lungs was due solely to the inhalation of stone dust, and that this injury in turn caused an enormous predisposition to tuberculosis, accounting for the large proportion of miners dying from tubercular phthisis. In 1915 Collis (7) incriminated free silica alone, and it is upon his thesis that our modern concepts of the cause of silicosis are based.

Pathology: Gardner (23, 25), perhaps more than any other one person, has clarified the pathology of the pneumoconioses. Inhaled dust first exerts its influence on living cells primarily within the bodies of the alveolar phagocytes, and it is here that fundamental differences due to the physicochemical composition of the irritant become evident. Inert substances, in which category the vast majority of dusts belong, provoke no structural changes within the cells. In contradistinction, free silica ex-

erts a specific toxic effect. Degenerative changes, easily confused with those in the "epithelioid" cells of tuberculosis, quickly become evident. The enlarged cells contain visible lipoid. Their nuclei repeatedly divide, and giant cells comparable to the Langhans' giant cells of tuberculosis are formed. Eventually these migrating phagocytes concentrate the silica in and about the pulmonary lymphatics, where the toxic particles, either directly or indirectly through their released lipoids, stimulate connective-tissue proliferation, with the resultant formation of microscopic silicotic nodules situated in the immediate vicinity of the lymphatic trunks.

At this stage the only general influence of the disease thus far discovered is the increased likelihood that the more advanced stages of silicosis will result from the continued inhalation of silica-laden dust. After sufficient reaction has developed in the lymphoid tissues, the flow of lymph is retarded. The alveolar phagocytes, however, continue to take up fresh particles of dust but, due to their apparent inability to enter the lymphatic vessels, collect upon the walls of the air spaces proper. Once again, the silica exerts its specific effect, causing proliferation of connective tissue and the formation of parenchymal silicotic nodules. Microscopically the nodules are seen to be composed of hyaline collagen fibers (Fig. 1) and are evenly distributed throughout the lungs (Gardner, 25). Such, in brief, is the pathology of simple silicosis.

The modifications occurring from the inhalation of dusts containing mixtures of free silica and other minerals may be quickly passed. The primary pathology is the same, the essential difference being simply the result of coexisting silicosis and a benign pneumoconiosis, each of which alters to some extent the appearance of the other. It should be recalled, however, that some inert dusts, when mixed with free silica, cause varying degrees of retardation in the development of the silicotic process. At this time the use of aluminum deserves brief but special mention. Denny, Robson, and Irwin (14) were the

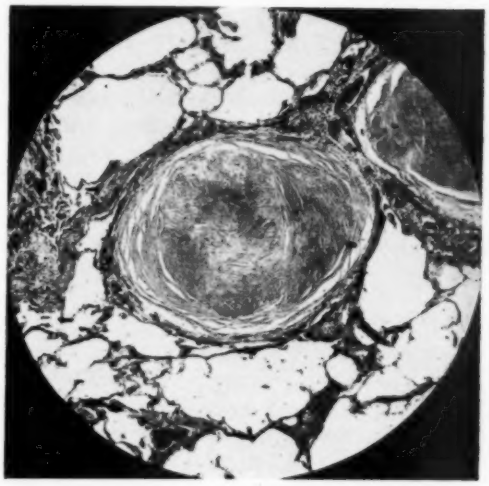

Fig. 1. The silicotic nodule.

first to announce the specific inhibitory effect of aluminum. Their animal experiments and those of others (26), some of which were conducted simultaneously in another laboratory, have demonstrated conclusively that metallic aluminum and aluminum hydrate, when given by inhalation, will prevent the fibrous reaction to quartz. The possible clinical applications of such a discovery are obvious, and have already stimulated considerable investigative work from the standpoint both of prophylaxis and of therapeusis. While a complete discussion of their present status is beyond the scope of this paper, it may be said that further evaluation is required and that aluminum therapy should in no circumstances be applied as a substitute for other and already recognized methods of dust control.

The alteration of the silicotic process when complicated by the presence of infection is not nearly so simple. The increased susceptibility to tuberculosis in man recorded by Merewether (37), and proved by the classic animal experiments of Gardner (19, 20), needs no recapitulation. Two facts, however, must again be emphasized: (1) that it is the presence of associated infection which accounts for most of the disability arising from silicosis,

and (2) that infection, when it occurs, may manifest itself in either of two ways, namely by the development of tuberculo-silicosis or of silicosis with tuberculosis.

Tuberculo-silicosis is common, and according to Brumfiel and Gardner (5), whose observations are adequately substantiated both clinically and pathologically, it is "a distinct disease entity with certain characteristics peculiarly its own, in that it is neither silicosis nor tuberculosis nor is it a simple summation of the two." It is the result of the interaction of tubercle bacilli and silica in the same area, with the resultant formation of tuberculous granulation tissue together with a modified type of silicotic reaction. Pathologically, it is characterized by the formation of slowly developing, well defined, hard or rubber-like areas of massive conglomerate fibrosis surrounded by a marked degree of emphysema. On microscopic section, nodules are found embedded within dense hyaline fibrous tissue which virtually obliterates the normal pulmonary structures. The tuberculous component of the process sometimes is identified easily by the presence of widespread caseation, but not infrequently it is only after painstaking search that isolated, non-caseous tubercles or occasional clumps of acid-fast bacilli are discovered.

Silicosis with tuberculosis, by comparison to tuberculo-silicosis, is rare, but it does occur in one of two forms: either (1) as the result of infection superimposed upon a progressive and still active silicosis or (2) as the result of infection superimposed upon an old and already stabilized silicotic process.

In the first instance the infection becomes acute, and its course is usually one of uncontrollable extension. In the second, tuberculosis develops upon a background of an already stabilized silicosis, in which the quartz particles are presumably completely isolated within their fibrous nodules and thus exert no effect upon the superimposed infection. We have then simply the coexistence of silicosis and tuberculosis within the same individual, but without modification or acceleration of either disease process by the other.

The effect of silicosis upon non-tuberculous infection is less well documented. It cannot be denied with finality that non-specific inflammatory reactions within silicotic lungs occasionally may be the precursors of conglomerate areas of fibrosis. Proof, however, is lacking, and the meager available evidence is opposed to such an assumption. Pierpont (46) has demonstrated that in his iron-mining area the incidence of pneumonia is no greater than in the general population, and that the behavior of the disease when it does occur is unaltered by an underlying silicosis. Similarly in rabbits it has been shown that silicosis exerts no effect upon their susceptibility to infection with Type III pneumococcus (57).

On the other hand, Gardner (25), after microscopic examination, was able to discover in only 60 per cent of cases showing massive conglomerate fibrosis indisputable evidence of tuberculous infection. Perhaps in most if not all of the remainder, the silicotic fibrosis had obscured the tuberculous component of the process, and it was his feeling that an underlying tuberculosis was the etiologic factor accounting for at least the majority of massive fibrous lesions.

Criteria for Diagnosis: The diagnosis of silicosis rests primarily upon a positive history of sufficient exposure to free silica dust plus the roentgenologic demonstration of characteristic deviations from the normal within the lungs. Physical and laboratory examinations are then required to exclude other conditions producing similar roentgenographic changes. Once the diagnosis is established, physical examination is required to determine the general physiological effect of the pulmonary condition and to determine whether any disability has resulted therefrom. Differences in individual incentive to work, the natural retardation of physiological responses with advancing age, and the accrued evidence to show that ordinary, slowly developing, simple silicosis is usually

in itself non-productive of a diminution in ventilatory capacity, all combine to make an accurate estimation of the latter an extremely difficult problem.

Simple Silicosis: It is within the scope of this paper to treat in detail only the roentgen manifestations of silicosis, but it must be emphasized that a history of adequate exposure to silicon dioxide-containing dust is the fundamental criterion for diagnosis. In all instances, therefore, the occupational history must be complete, and in doubtful cases a detailed study must be made of the industrial environment, including chemical and petrographic analyses of raw materials and settled dust, as well as estimations of the quantity and kind of atmospheric dusts. The current industrial practice of keeping accurate work sheets on all employees, together with records of periodic counts and analyses of all atmospheric dusts, will in the future greatly simplify this aspect of the problem, and may also, despite the ever-present factors of individual susceptibility, eventually lead to the establishment on a scientific basis of a truly safe level of exposure.

Perhaps in no other disease are the unit pathological lesions—discrete nodules of hyaline fibrous tissue—better reflected in the roentgenogram than in a well developed case of simple silicosis (Fig. 2). These nodules, uniformly distributed throughout the pulmonary parenchyma, form a characteristic shadow pattern, and *the demonstration upon the roentgenogram of this generalized nodulation is, from the radiologist's point of view, fundamental to the diagnosis.* There may or may not be associated enlargement of the hilar lymph nodes, despite the fact that it is in the lymphatic tissues that the earliest silicotic nodules have been shown to develop. These early nodules, however, by their very fibrous nature, are destined to cause eventual contraction, and in cases of slowly developing silicosis it may no longer be possible to demonstrate hilar lymph node enlargement by the time the parenchymal nodules are grossly visible.

Following the fulfillment of the above-described criteria for diagnosis—historical, roentgenographic, and physical—it has become convenient in certain instances to use some classification descriptive of the variations encountered in the development and maturation of simple silicosis. *The use of such a classification, however, should not imply that all cases of silicosis develop in a measured fashion through various stages, or that once a given stage is reached the next must inevitably follow, nor should it be used as a mechanism for the estimation of disability.* A grouping useful to many, in the development of which Gardner and Sampson had a prominent role, subdivides the disease into three stages according to the number and size of the nodular shadows. In Stage I, or first-degree silicosis, the nodules are barely visible and are associated with a preservation and at times exaggeration of the linear markings (Fig. 3). In Stage II, the nodules are from 2 to 3 mm. in diameter and are of sufficient size to largely obscure the linear markings (Fig. 4). Gardner (22) has aptly likened this latter phenomenon to the leaves on a tree which as they mature obscure the branches to such an extent that they become scarcely visible. In Stage III, the nodules are

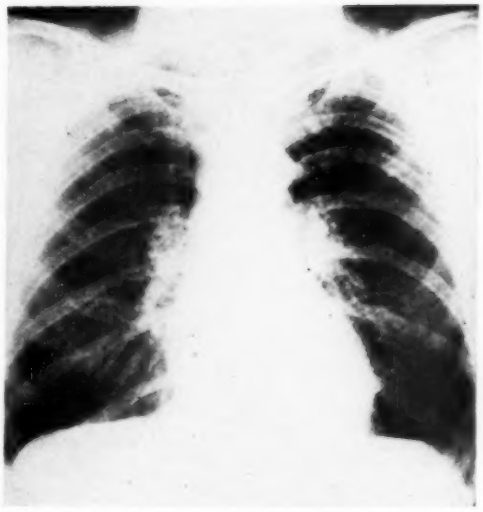

Fig. 2. F. B., age 55. The generalized nodulation of simple silicosis.

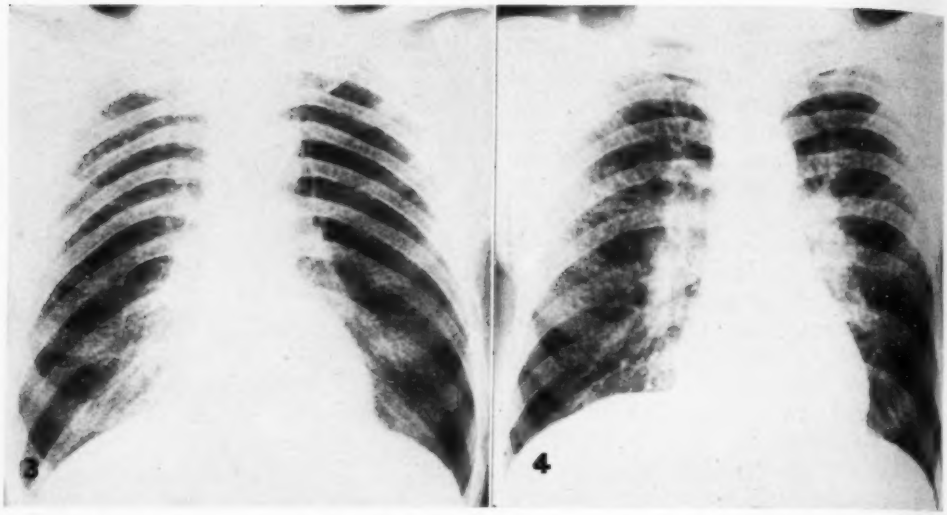

Fig. 3. F. A., age 65. Simple silicosis occurring in an iron miner. The early nodulation is a little more prominent than in Figure 2.

Fig. 4. G. H., age 36. Simple silicosis occurring nine years after onset of exposure in an iron miner primarily engaged in shaft sinking through "hard rock." The nodulation is more prominent than in Figure 3. Note prominent hilar shadows.

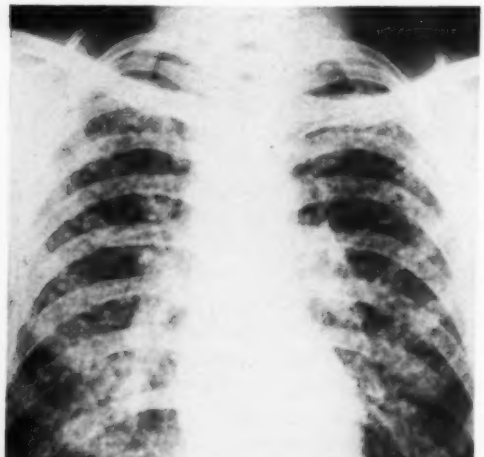

Fig. 5. A. Z. Simple silicosis. The shadows are more prominent than in Figure 4. Note multiple small areas of coalescence, presumably the result of "coalescence by contiguity."

greater than 3 mm. in diameter, and many attain a size of 5 or 6 mm. (Fig. 5). In this last group there may, in addition, be seen multiple small areas of coalescence which may lead to a suspicion of coexisting infection. In these cases, however, the areas of coalescence are not massive but are small and widely scattered, indicating that they may be the result not of old infection but of conglomeration by simple contiguity. We are in accord with the use of such a classification, purely as a matter of convenience. *Lest any misconception arise, however, it is reiterated that it is the nature of the lesion that should invariably be emphasized rather than its stage of development.*

Silicosis with Infection: Thus far only the criteria for the diagnosis of simple silicosis have been reviewed, leaving for description the roentgen characteristics of that large and most interesting group of all, in which there is either direct or indirect evidence of coexisting infection. The rationale for further division into the subgroups tuberculo-silicosis and silicosis with tuberculosis has already been explored, with emphasis placed upon the concept that tuberculo-silicosis is a separate and distinct, chronic disease entity resulting from the prolonged interaction of two disease processes, but differing radically in its behavior from either occurring alone.

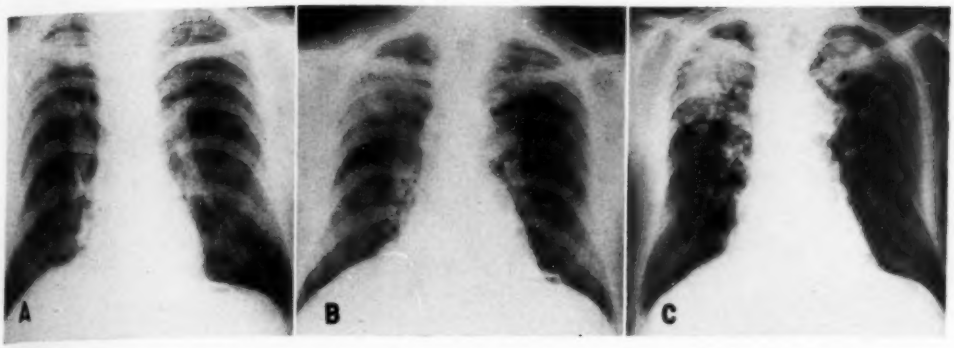

Fig. 6. S. P., age 47. Development of conglomerate nodulation in tuberculo-silicosis. A. Aug. 21, 1934: Generalized nodulation with evidence of "concentration" of the nodulation in the right apex and linear strands of fibrosis in the left. B. May 19, 1939: Further "concentration" with "coalescence" of the nodulation in the right upper lung field and "concentration" in the left about the foci of fibrosis. C. June 28, 1944: Bilatera "massive shadows" of conglomerate fibrosis. Note deviation of trachea to the right.

The roentgen manifestations of tuberculo-silicosis are protean and yet distinctive. Early in its evolution there are characteristically present linear strands of fibrosis, presumably the result of previous infection, which however may be so fine as to be almost or completely obscured by the accompanying nodulation. In due course, serial roentgenograms reveal evidence first of concentration and later of coalescence of the nodulation about these foci of fibrosis. Newly developed areas of coalescence may extend to the pleural surface of the lungs, but if the disease remains chronic they inevitably contract to form the dense, well delineated "massive shadows" or areas of conglomerate fibrosis so typical of tuberculo-silicosis (Fig. 6). These are located most often in the upper lung fields, but may radiate outward from the region of the hilum, occur as rounded masses deep within the lungs, or appear as wedges with their bases directed peripherally. Commonly, these areas of conglomerate fibrosis continue over the years to increase slowly in size, incorporating within themselves more and more of the individual silicotic nodules from other portions of the lungs, until finally one may have as the end-result either single or multiple, unilateral or bilateral, massive shadows of conglomerate fibrosis. These may be so extensive as to destroy completely the ordinary identifying characteristics of both the tuberculosis and the silicosis, and they are invariably productive of an advanced degree of surrounding pulmonary emphysema. Since the affected individuals are not toxic, it is this latter which accounts for their obvious and often high degree of disability.

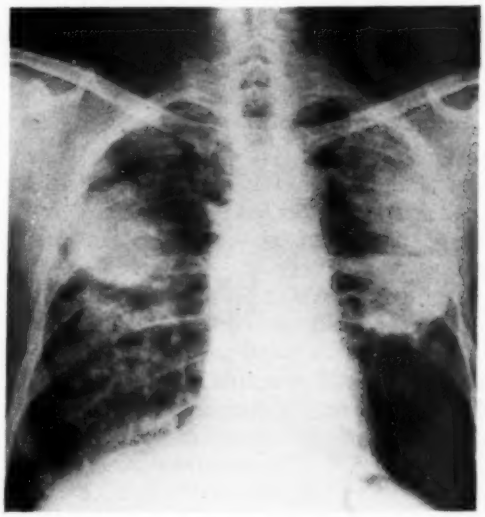

Fig. 7. F. G., age 63. The massive shadows of conglomerate fibrosis seen in tuberculo-silicosis. Note that the generalized nodulation has been virtually obliterated and that the lungs are markedly emphysematous.

Only rarely is one sufficiently fortunate to see the evolution of the entire process in a given individual. It would seem, how-

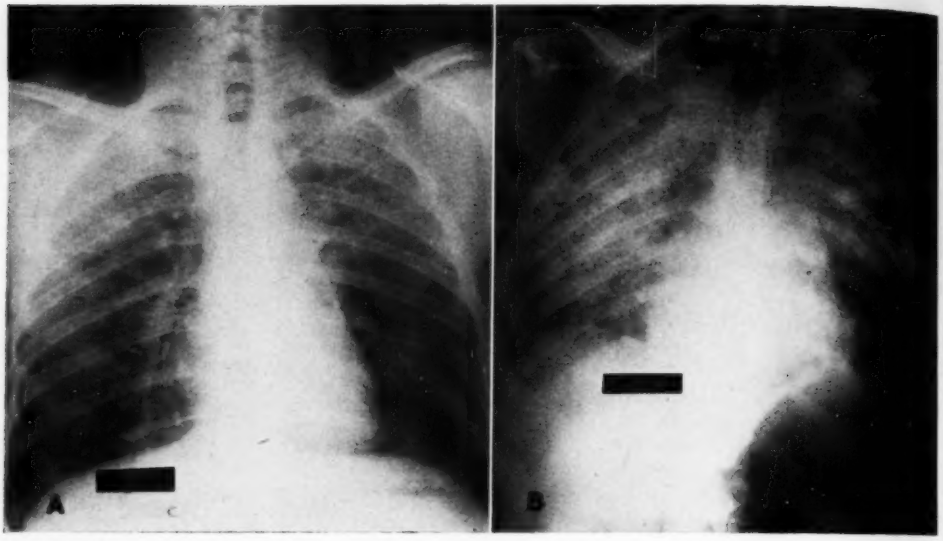

Fig. 8. J. B. Silicosis with tuberculosis, in which both the silicosis and the tuberculosis are active. A. May 13, 1931: Generalized fine nodulation with "mottling" indicative of infection in both upper lobes. B. Oct. 3, 1931: Postmortem film five months later, showing rapid extension of the infection.

ever, that the pathologic evidence is sufficient, and that adequate numbers of cases have now been followed by means of serial roentgenograms over a period of years, to warrant a presumptive diagnosis of tuberculo-silicosis either upon the visualization of nodulation with concentration, coalescence or conglomeration, or, when bilateral, upon the demonstration by themselves of large areas of conglomerate fibrosis (Fig. 7). Limited reservations must of necessity be entertained, however, until the case for or against non-tuberculous infection as the etiologic agent in the production of conglomerate fibrosis is definitely proved.

The behavior of many cases of tuberculo-silicosis would make it appear that the tuberculous component of the process is for a time held in check by the surrounding fibrosis. It remains a potential source of danger, however, and may become active at any time. Such activity manifests itself on the roentgenogram by the development of mottling and, once established alters, by acceleration of the fatal outcome, the entire course of the disease. It is still true, therefore, that a high percentage (though by no means all) of persons with tuberculo-silicosis ultimately die of tuberculosis.

Silicosis with tuberculosis, as previously indicated, may occur in either one of two forms, the clinical course and roentgen behavior of which are as distinctively different as is their pathology. Early in their development they may present an extremely difficult problem in diagnosis because of one's inability, except upon the basis of preceding serial roentgenograms, to formulate any estimate of the activity of the underlying silicotic process. In both groups the infectious component is first identified by the presence on the roentgenogram of single or multiple, usually apical, ill-defined areas of infiltration or mottling, superimposed upon a background of discrete nodulation. The subsequent behavior, however, is radically different.

In the first group—those in which we have fresh infection, either new or arising from the reactivation of a latent focus, superimposed upon a progressive and still active silicosis—the quartz is incompletely encapsulated by the still immature sili-

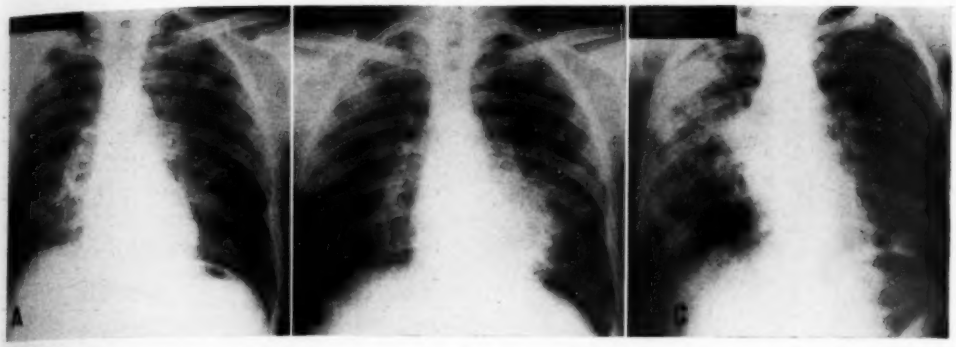

Fig. 9. R. B., age 33. Perinodular type of silicosis with tuberculosis. A. Jan. 25, 1933: Generalized nodulation with associated small foci of mottling in apices and at left base. B. April 18, 1933: Increase in the extent of mottling together with increase in size and loss of definition of the nodular shadows. C. June 11, 1933: Further extension of infection with cavity formation on the right and emphysema on the left. Film C was made one month prior to death.

cotic fibrosis, and retains its ability to exert its specific effect as a tissue poison. When the silica concentration is high, tiny foci of necrosis within the nodules occur, providing an ideal medium for the growth of tubercle bacilli; but even when the silica content is not excessive there is in some occult manner produced an environment eminently favorable to their multiplication (20). Serial roentgenograms exhibit new areas of mottling and local extensions of the original foci, about which the silicotic nodules may become extremely abundant (21) (Fig. 8). In some, the so-called "perinodular type" (Fig. 9), there occurs, probably as a result of massive superinfection, a rapid enlargement with loss of definition of each nodule throughout both lungs, due to the development of an intense surrounding zone of collateral inflammatory reaction. Minute foci of caseation are usually present, and cavitation does occur, but by comparison with the general evolution of the process it is a relatively late phenomenon. While rarely several years may elapse before toxic symptoms supervene, the general tendency is toward uncontrollable extension to death before there is opportunity for the chronic changes of tuberculosilicosis to occur.

In the second group are the unusual but existent cases in which silicosis and tuberculosis occur together but act independently. As previously indicated, it is presumed that in these cases the silicosis has healed with the formation of such densely fibrous nodules that the quartz is completely walled off and thus cannot exert its peculiar effect upon the superimposed tuberculous infection. The infection, observed by means of serial roentgenograms, is seen to behave typically as it does in non-silicotic subjects.

Asbestosis

Asbestosis is the second of the recognized specific pneumoconioses. Since, however, its roentgen manifestations in no way simulate those occurring in silicosis, the criteria for its diagnosis are not reviewed.

DIFFERENTIAL DIAGNOSIS

Any exposition of the criteria applicable to the diagnosis of the specific pneumoconioses, and of silicosis in particular, must include other conditions which not infrequently make the problem of differential diagnosis extremely difficult. Some of these are so familiar as to require but brief mention; others, either because of their unusual interest or because of the frequency with which they are misdiagnosed as silicosis, will be considered in some detail.

First in order of consideration are the benign pneumoconioses, and second, the many pulmonary diseases productive of

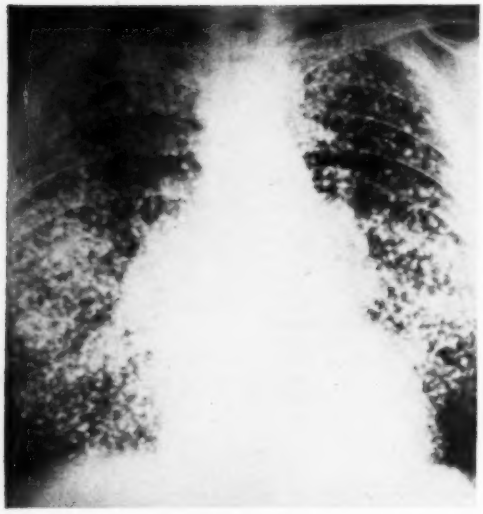

Fig. 10. Dense pseudo-nodulation of baritosis. No respiratory symptoms whatever were present. The condition was found in a routine investigation of workers in baryta ore. Compare this appearance with that seen in pseudo-nodulation due to inhalation of tin oxide, as shown in Figure 13.

roentgen changes similar to those of silicosis but unassociated with the inhalation of dust.

The Non-Specific Pneumoconioses

Under the heading "non-specific pneumoconioses," attention is directed to the pulmonary reactions resulting from the inhalation of all types of mineral dust which are incapable of stimulating within the lungs the development of progressive fibrosis. Anthracosis, siderosis, as well as the reactions to the inhalation of cement, gypsum, and the various silicates, with the exception of asbestos and possibly talc, are all included.

The alveolar phagocytes, regardless of the composition of the inhaled dust, tend to concentrate the particles within the lymphoid tissues of the lungs and mediastinum as well as in the areolar tissues about the perivascular lymphatic trunks. Excessive accumulations may excite a low-grade chronic inflammatory reaction which is non-progressive but which may be productive of small amounts of grossly invisible cellular connective tissue. The only secondary effect is the appearance of emphysema, microscopic in its proportions and of no clinical significance (25). Roentgenographically there may be some increase in prominence of the normal linear pulmonic markings, but with the exception of those "roentgenologic conditions" productive of a pseudo-nodulation and resulting from the inhalation of inert but radiopaque dusts, no *specific* deviations from the normal can be identified. Increasing experience will doubtless lead to the recognition of others, but to date those in the latter category to receive consideration are baritosis, siderosis, and the changes occurring due to the inhalation of tin oxide.

Baritosis, originally described by Arrigoni (3), results from the inhalation of barium sulfate, and occurs chiefly among the baryta miners in Italy, although one of us (Pendergrass, 43) has reported a small incidence among workers in a Pennsylvania plant. In baritosis there is no respiratory incapacity, the only evidence of the presence of the mineral being the demonstration upon the roentgenogram of sharply circumscribed nodules evenly distributed throughout the lung fields (44) (Fig. 10). Duplication of the condition in the experimental animal is unproductive of fibrosis, indicating that the nodulation demonstrable in roentgenograms results from the direct visualization of compact collections of radiopaque particles (25) within the lungs.

Siderosis, an analogous condition, occurs as the result of a number of industrial processes, chief among which are electric arc-welding, metal-grinding, silver finishing, and possibly boiler-scaling. Collis (8) in 1923 suggested that errors in the diagnosis of silicosis in iron miners might be made, due to the radiopacity of iron oxide. Subsequently, but without the benefit of clarifying pathological material, Doig and McLaughlin (15) in 1936 reported the occurrence of fine nodulation in 6 of 16 electric arc-welders. In 1938, Enzer and Sander (17) described similar findings in 5 of 26 electric arc-welders, who had worked for an average of nine-

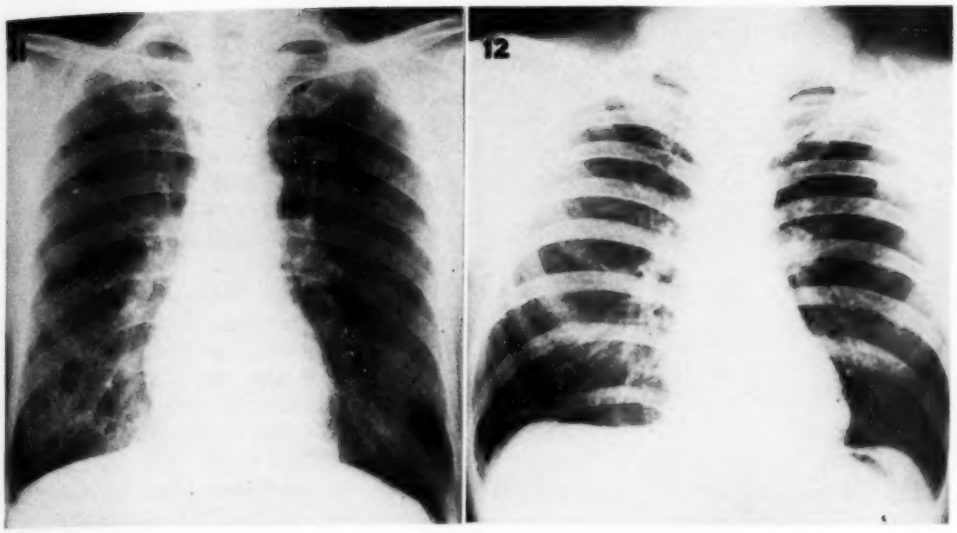

Fig. 11. S. M., age 58. Siderosis occurring after fourteen years of enclosed electric arc-welding. Note the generalized pseudo-nodulation with, however, a preservation of the linear markings.

Fig. 12. Siderosis (benign pneumoconiosis) occurring in a metal grinder who had worked in a steel-bearing company for twelve years. He had no complaints. The pseudo-nodulation in the lung fields due to iron oxide was found in a general survey of the industry. This patient does have an old lesion in the left upper lobe which is suggestive of a tuberculous lesion. The pseudo-nodulation of siderosis simulates that found in silicosis, and pulmonary hemosiderosis. Compare with Figures 2 and 18.

teen years using bare metal rods containing 99 per cent iron and 1 per cent free silica, and in one case presented necropsy findings to indicate that the roentgen changes were a direct consequence of the collection of radiopaque iron oxide particles within the lungs. Sander (52) states that Enzer has since obtained three additional and confirmatory autopsy cases.

In 1945, entirely similar roentgen findings were reported by one of us (Pendergrass, 44) in 4 of 10 metal-grinders who had worked from twelve to seventeen years in a plant shown to be free of a silica hazard. The metal ground was used in the manufacture of bearings and was identified as chrome vanadium and chrome molybdenum tool-steel containing about 98 per cent iron, 1.8 per cent alloy, and 0.2 per cent silica. For the grinding process, artificial abrasive wheels, recognized as innocuous from the standpoint of a silica hazard and composed of bakelite, carborundum, and aluminum oxide, were used exclusively throughout the occupational lives of the affected persons.

More recently, the occurrence of identical roentgen findings in silver-polishers has been reported from England (35). Quite pure and finely divided iron oxide in the form of either "rouge" or "crocus" is used in the final finishing of silver, and when applied to revolving "dollies" is productive of considerable dust, consisting primarily of iron oxide contaminated with metallic silver, the latter also being radiopaque. Four men, employed as silver-finishers for periods of twenty to forty years, were examined. Chest roentgenograms of all presented the changes to be described below, and a subsequent autopsy on one revealed only particulate collections of iron oxide with small amounts of silver within the lungs.

A similar condition has been described as occurring in boiler-scalers (9, 16, 55). Here, however, there may be an associated silica hazard, the elimination of which is required before the changes seen can be properly attributed to siderosis.

Pathologically, in siderosis there is gross evidence of pigmentation, the ferrous

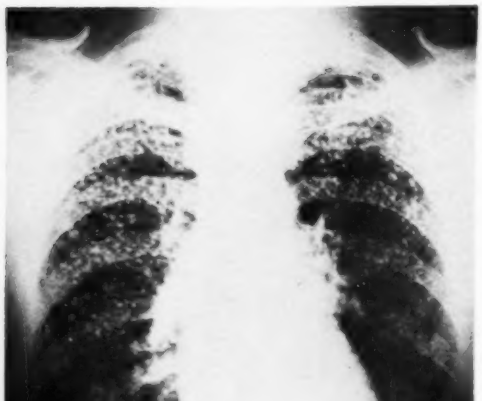

Fig. 13. Roentgenogram of a man about 45 years of age who had bagged tin oxide for fifteen years. There are discrete densities throughout both lungs which are regarded as pseudo-nodulation of a benign pneumoconiosis due to tin oxide. The shadows are denser than those seen in most cases of silicosis. Only the occasional case of silicosis shows such dense nodulation. The appearance is more like that seen in baritosis (see Fig. 10). The hilar lymph nodes contain considerable opaque material.

nature of which may be demonstrated by proper staining. Histologic sections show the pigment to be distributed chiefly in the perivascular lymphatics, the subpleural spaces and the interalveolar septa. It is the heavy accumulation in the perivascular lymphatics of the iron oxide pigment, in itself radiopaque, which accounts for the roentgen findings. At no time have any reactive phenomena, provocative of fibrosis within the cells, been described.

The pulmonary changes in siderosis, as reflected in the chest roentgenogram, cannot from the film alone be distinguished from those already described in detail as occurring in simple silicosis (Figs. 11 and 12). They are, therefore, simple of definition and consist of discrete nodular densities distributed uniformly throughout both lungs, without hilar enlargement but in some cases with an associated reticulation resulting from an increased prominence of the linear markings.

Pseudo-nodulation due to inhalation of tin oxide has been reported by Pendergrass and Pryde (45). They recorded a case which had been studied by Dr. Hollis E. Potter of Chicago. The patient was a 45-year-old man who had worked at a single job of bagging tin oxide for fifteen years. There was no disability. The roentgenogram showed diffuse dense pseudo-nodulation throughout both lungs similar to that observed in baritosis (Fig. 13) and considered to be a benign pneumoconiosis. Chemical analysis of the tin oxide showed it to be 96.5 per cent tin oxide, while the remaining 3.5 per cent contained aluminum, iron, and sodium. No silica was found. Experimental studies of the material placed in a dog's lung and in phantoms showed that its density was sufficiently great to produce shadows equal to or greater than those produced by iron. The pseudo-nodulation produced by tin oxide is not to be confused with the pneumoconiosis reported in the tin miners of Cornwall (28); the industrial hazard among them was one of silicosis.

It seems quite obvious that a detailed occupational history is fundamental to the differential diagnosis of silicosis and the pseudo-nodular types of the benign pneumoconioses.

Talc Pneumoconiosis

It has already been indicated that the silicates, with the exception of asbestos and possibly talc, belong in the category of inert dusts. Asbestos, a fibrous silicate, is productive of a specific pneumoconiosis characterized by the formation of a progressive interstitial pulmonary fibrosis. Talc, also a silicate, with certain physical characteristics in common with asbestos, requires more specific evaluation.

The available experimental evidence would indicate that talc alone is incapable of producing a progressive fibrosis (24, 30). The criticism has been advanced, however, that the inhalation experiments were of insufficient duration to define conclusively the effect of long continued industrial exposure, this latter being fundamental to the development of specific changes

(54). Siegal reports no case with less than ten years' exposure, but then records an incidence of 14.5 per cent "talc pneumoconiosis."

Roentgenograms are described as showing a bilateral diffuse haziness or "ground-glass" appearance, with some tendency to parahilar and subapical localization, and, in some cases, with the presence of an ill defined nodulation and/or conglomerate areas of fibrosis (Fig. 14) leading to a suspicion, as yet unproved, of underlying infection (39, 54). Siegal (54) further directs attention to an occasional right-sided predominance and to a rarely demonstrable blurring or "shagginess" of the cardiac silhouette, reminiscent of asbestosis. He also describes in detail the occurrence of "pleural plaques," long associated with the inhalation of talc.

The similarity of the described roentgenographic manifestations to those of asbestosis is quite striking, and the occurrence of an asbestosis-like reaction following prolonged industrial exposure to talc would seem unlikely. Further controlled investigation, designed to eliminate the possible complicating factors of quartz-contaminated dust and infection, is, however, imperative before concluding with finality that the roentgen changes are the reflection of a specific and progressive fibrosis, and that talc is the sole etiologic agent in their production. In this regard, it seems quite probable that the described coexistent nodulation may be silicotic in origin. In the reported autopsy cases (39) there had been other opportunities for the inhalation of dusts presumably contaminated with silica, and in the mining of talc itself similar exposures have not been excluded.

Vanadium Pentoxide

There is another industrial disease due to the *toxic effects* of *vanadium pentoxide* (60). The authors have had no personal experience with this but a short discussion is included for completeness.

Vanadium is a silvery white metal rarely encountered in its pure state. The ores

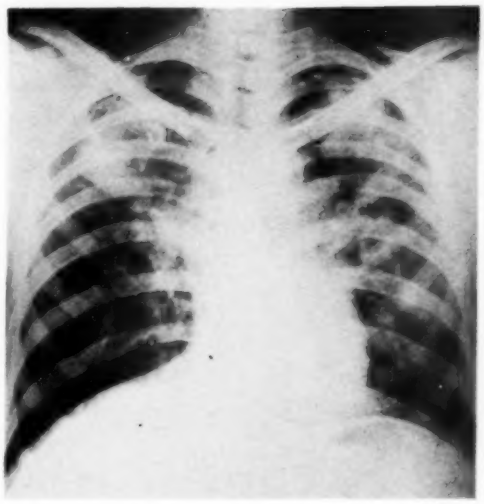

Fig. 14. Talc pneumoconiosis in a man 51 years of age, who worked in a talc mine for thirteen years. There are massive shadows in the upper thirds of both lung fields, and coalescent shadows in the middle third. One sees very little evidence of nodulation. Illustration shown through the courtesy of Dr. Arthur Hobbs.

are distributed mainly in Peru, South Africa, and Rhodesia (60). The chief uses of vanadium are to raise the hardness and malleability of steel and to increase its fatigue-resisting properties. Vanadium pentoxide, a yellowish red powder, is used as an oxidizing agent in the conversion of naphthalene to phthalic anhydride and in place of platinum in the modified contact process of sulfuric acid manufacture (60).

It had long been known that vanadium pentoxide dust would cause bronchitis among workers, but the full significance of the condition was not appreciated until the report of Wyers appeared (60). He has observed at least 50 workers, men and women, some of whom showed reticulated shadows in the lower lung fields. It is not known whether these shadows are due to accumulation of dust in the air sacs or fibrosis. Vanadium workers complain of paroxysmal cough and pains in the chest, and have a tenacious sputum, which may be blood-streaked. They may develop emphysema. Other signs of the condition are those of systemic intoxication, which may be evi-

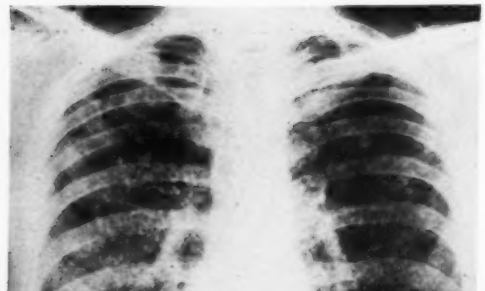

Fig. 15. F. T. Generalized hematogenous tuberculosis. The nodular pattern closely simulates that seen in silicosis. The occurrence of scattered foci of mottling, however, serves as an aid to the differential diagnosis.

denced by diarrhea, anorexia, emaciation, visual defects, paralysis, vertigo, and convulsions.

Other and Confusing Causes of Nodular Densities within the Lungs

Tuberculosis: Tuberculosis, following an hematogenous dissemination, presents on the roentgenogram evenly distributed nodular densities throughout both lungs, occasionally indistinguishable from those occurring in simple silicosis (Fig. 15). Except in these cases, difficulty in the differential diagnosis between tuberculosis and silicosis seldom occurs, but in them the distinction must be made upon the basis of history, physical examination, and laboratory findings. Frequently an additional aid is the identification, in tuberculosis, of an accompanying localized infiltrate or cavity, without, however, evidence of conglomerate fibrosis of the type already described as occurring in tuberculo-silicosis.

Histoplasmosis: Darling (10, 11, 12) in 1906 and 1907 recorded three cases of a generalized and fatal protozoan infection, subsequently identified as histoplasmosis, which produced pseudo-tubercles in the lungs and areas of focal necrosis in the liver, spleen, and lymph nodes. Further reports (6, 33, 38, 40, 50, 51, 59, 61) in more recent years have shown the disease to be world-wide in distribution, but most common in the east-central portion of the United States; have adequately documented its pathology and clinical course;

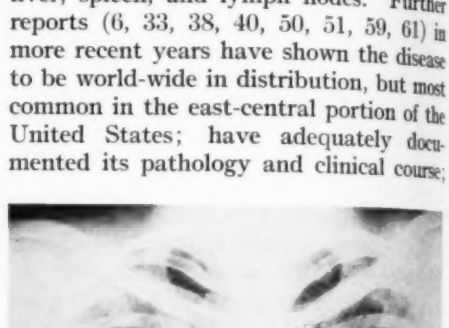

Fig. 16. Histoplasmosis in a 26-year-old male. There are multiple lesions throughout both lung fields simulating those found in the perinodular type of silicosis (see Fig. 9). The sputum was negative, tuberculin skin test was negative, and systemic review showed nothing of significance. The histoplasmin intradermal test was positive, showing an erythema 15 and induration 8. This man is a patient of Dr. David Cooper, and the illustration is shown by his permission. Dr. Cooper reports that the case has been followed from 1941 to 1946 and most of the lesions have disappeared except for a few scars.

and have offered evidence in support of the thesis that it is not invariably fatal but that it in all probability exists most commonly in a benign and asymptomatic form. DeMonbreun (13) in 1932 proved its fungous origin by identifying *Histoplasma capsulatum* as the causative organism.

The symptoms of histoplasmosis, when it is clinically manifest, are protean, being those of a generalized infection of the reticulo-endothelial system, for which Meleney (36) suggests the name "reticulo-endothelial cytomycosis." Of primary

interest in this presentation, however, is the 20 per cent (33) occurrence of significant lung lesions. In some of these the roentgen findings closely simulate those of pulmonary tuberculosis, consisting of apical infiltrations with or without cavity; in others, miliary lesions 5 to 15 mm. in diameter are evenly distributed throughout both lungs (Fig. 16). It is these latter which may resemble silicosis, and make necessary the inclusion of histoplasmosis in the differential diagnosis of the nodular pneumoconioses.

Also, in the areas endemic for histoplasmosis, the incidence of "disseminated miliary calcifications" is relatively more frequent than in the country at large (34). While in such cases the nodules characteristically vary slightly in size, are of irregular distribution, and lack an uncalcified periphery (Fig. 17), their appearance is such that they may rarely require differentiation from silicosis with central calcification of the nodules.

The Mycotic Infections: There are a number of conditions, such as fungus infestations, that may simulate the various manifestations of silicosis. One of the important points in arriving at the diagnosis is for the radiologist to bear these in mind. Some of the more frequent infestations seen by us are mentioned.

In *moniliasis*, in which the chief pathogen has been found to be *Monilia albicans*, the roentgenogram shows irregular areas of infiltration which tend to become nodular. The appearance is similar to that in simple silicosis with nodular predominance. Fawcitt (18) has called attention to finding bronchomycoses as a complication in hematite iron-ore workers.

Sporotrichosis is due to a Streptothrix. In the cases that we have observed, the appearance is identical with nodular silicosis.

The roentgen appearance in *actinomycosis* may be that of a bronchopneumonia. The process may be diffuse or localized to one lobe. It may be confused with silicosis with infection.

It is sometimes difficult to establish the true diagnosis of a fungus disease, but every effort must be made to exclude the lesions that simulate silicosis before making a definite diagnosis of the latter.

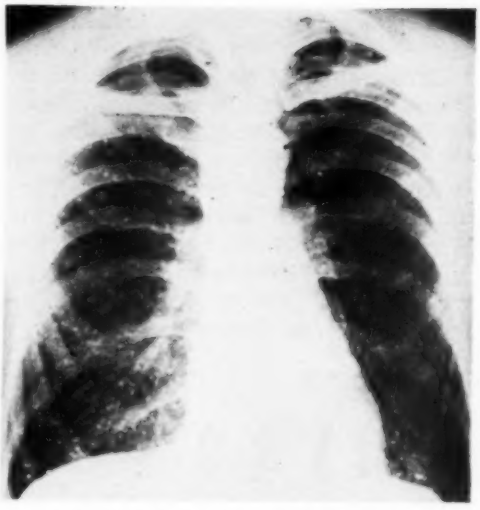

Fig. 17. Disseminated miliary calcifications occurring in the lungs of an iron miner.

Pulmonary Hemosiderosis: Pulmonary hemosiderosis clearly demonstrable in roentgenograms as diffuse nodulation (2), similar to that produced by silicosis, is said to occur in some patients with mitral stenosis (44, 53). Scott (53), in an excellent paper, has discussed the subject in detail and has shown, we believe, that hemosiderin is responsible for the shadows in the roentgenograms (Fig. 18). In our patient there was a preceding rheumatic fever. The shadow pattern is similar to that produced by silicosis or the pseudonodulation of benign pneumoconiosis.

Polycythemia Vera: Polycythemia vera in patients with cyanosis and vascular engorgement may present a markedly increased prominence of the vascular shadows in the lung. Vessels seen in an axial plane simulate the nodulation found in silicosis. There are other shadows in polycythemia vera of unknown origin which simulate the shadows produced by conglomerate fibrosis. The history, physical examination, and blood count will assist in the differential diagnosis.

Metastatic Carcinoma: Carcinomatous metastases may resemble the nodular and conglomerate shadows of silicosis with and without infection. Primary carcinomas arising in the gastro-intestinal tract and kidney tumors account for the great majority of such metastases, but carcinomas arising from other sites may be responsible. Here again the history and clinical findings should assist greatly in determining whether a malignant process is responsible for the abnormal shadow pattern.

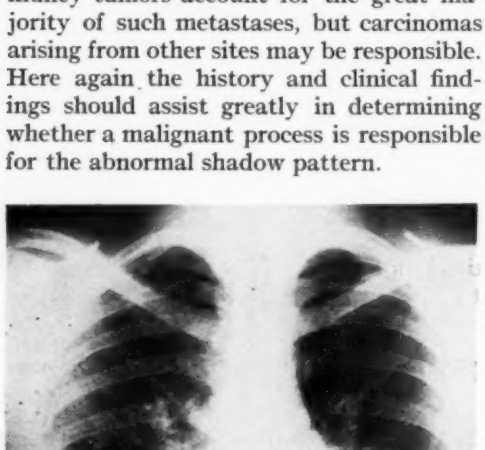

Fig. 18. Pulmonary hemosiderosis in an Italian male who has mitral stenosis. He has been followed for at least ten years. The pseudo-nodulation is similar to that seen in simple silicosis (see Fig. 2) and siderosis (see Fig. 12).

Boeck's Sarcoid: Boeck's sarcoid is primarily a systemic disease, classically presenting widespread involvement of the lymph nodes, viscera, osseous system, and skin. Commonly, however, its clinical manifestations occur in various combinations, leading to its separation into types, as the uveoparotid fever of Heerfordt and Mikulicz's syndrome. Similarly, there is a fairly large group—17 in Reisner's series of 35 cases (49)—in which associated lymphadenopathy and pulmonary involvement constitute either the most conspicuous or the only discernible manifestation.

The manifestations in chest roentgenograms are in turn extremely variable as to extent, distribution, and character, depending largely upon the phase of evolution of the disease process at the time of examination. For convenience of description, and without implication that the process is at any time static, both Reisner (49) and Bernstein (4) have subdivided the roentgen findings into several types. In attempting to identify the various forms of the disease, a free use of both classifications is made: (1) In some cases the only abnormality demonstrable on the roentgenogram is a bilateral, usually symmetrical enlargement of hilar and tracheobronchial lymph nodes. (2) The so-called "miliary sarcoidosis" is characterized by the presence of widespread nodular densities throughout the lungs (Fig. 19); in these the nodules are usually quite uniform in size and distribution, but may at times exhibit a moderate tendency to coalescence and be most dense in the middle thirds. Commonly there is easily demonstrable hilar lymphadenopathy but, depending upon the phase of the disease, this may or may not be present. (3) A third group includes those cases in which there is hilar lymphadenopathy together

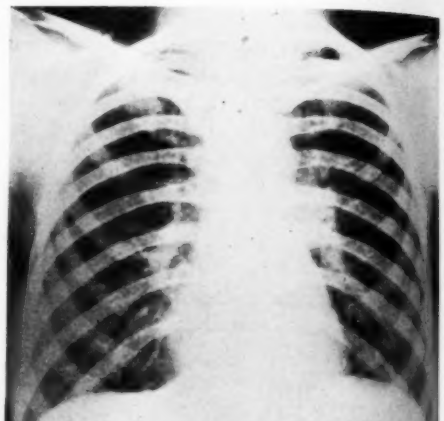

Fig. 19. Disseminated lesions of pulmonary sarcoidosis in a 36-year-old colored female. The lesions simulate those seen in simple silicosis and could readily be confused.

with a string-like infiltration radiating outward from the hila into the pulmonary parenchyma. These string-like shadows appear perivascular in distribution and may be combined with a generalized nodulation such as has already been described. (4) A fourth type presents roentgenographically diffuse parenchymal infiltrations visualized as well demarcated but irregular and often contracted areas of increased density, having the appearance of fibrosis. Hilar lymphadenopathy is a variable finding, as is an associated background of increased linear markings and nodulation.

In all forms of this disease the pathological lesion is the non-caseating tubercle. The clinical course, however, is variable though inevitably chronic. The first and second types above described may represent an early and reversible stage, and both show a pronounced tendency to resolution. King (32) has reported complete clearing within an average of twenty-two months in 23 of 37 cases of pulmonary sarcoidosis, but does not specify the type of involvement. In the third and fourth types the changes are at least partially irreversible. Some degree of resorption may occur, but there inevitably remains a residuum of increased linear markings and at times a massive contracting fibrosis. The latter leads to varying degrees of disability, and in some cases to a fatal termination, the commonest causes of which are the development of or transition into a typically caseating pulmonary tuberculosis or the development of cor pulmonale (27, 49).

The roentgen appearance of Boeck's sarcoid and certain of the pneumoconioses, including silicosis, is occasionally identical. The nodulation in the miliary form may be indistinguishable from that of silicosis and the pseudo-nodular types of the benign pneumoconioses, and the late fibrous reactions may rarely simulate the picture of tuberculo-silicosis. In all such cases, the differentiation rests upon a critical evaluation of the historical, clinical, and laboratory data. The distinction, however, is usually not difficult, since in sarcoidosis one is commonly led to the correct impression by the presence of marked lymphadenopathy, by irregularities in the distribution and character of the pulmonary lesions, or by the presence of other and extrapulmonary lesions.

Chronic Pulmonary Granulomatosis in Beryllium Workers: The recognition of a new pulmonary disease appearing in workers engaged in certain industrial processes requiring the use of beryllium, or one of its compounds, is attracting increasing attention. This condition may present in the roentgenogram a pattern strikingly similar to that seen in silicosis. Affected individuals have, as a rule, been employed in the manufacture of fluorescent lamps, fluorescent powders, neon signs, or beryllium copper alloys, or have been engaged either in the extraction of beryllium from the ore or in projects of a research nature requiring the use of its compounds.

At least two rather distinctive and entirely different reactions have been described. The first of these, with which Van Ordstrand and his associates (56) in Cleveland have had the widest experience, is an acute chemical pneumonitis. Its roentgenographic characteristics, however, are entirely different from those of silicosis and require no elaboration in a discussion of the differential diagnosis.

The second type of reaction, recently labelled at the Sixth Saranac Laboratory Symposium as "chronic pulmonary granulomatosis occurring in beryllium workers," has been well described by Sosman and Wilson in a report from Hardy and Tabershaw (29), by Pascucci (41), and more recently again by Wilson (58). Its roentgen manifestations are extremely protean and for adequate description require some attempt at classification. As a consequence, two (41) or three (29) types or stages—granular, reticular, and nodular—are recognized. Granting the possibility that the various bizarre forms of the disease may represent different phases in its evolution, subdivision into types rather than stages would seem wiser until more

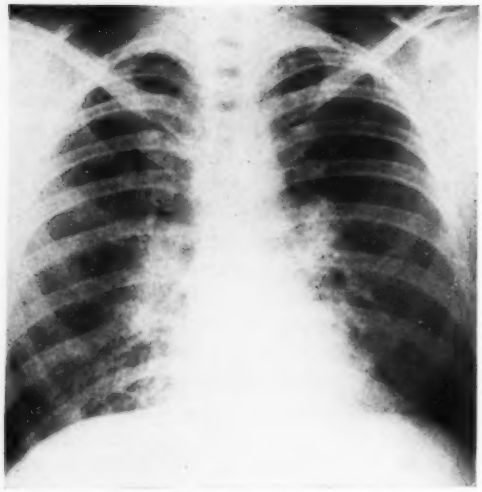

Fig. 20. H. B. Nodular type of chronic pulmonary granulomatosis occurring in a beryllium worker.

extended observation enables us to detect a certain general pattern in the developmental cycle. To date, in most cases one is unable to demonstrate a distinct transition from one form to another, and there is no clear-cut gamut of stages through which any given case must pass. In contradistinction, there is some indication, as yet meager, that the types now recognized are all late manifestations and that, prior to the development of chronic granulomatosis, there may be a preliminary and perhaps transitory stage comparable to the acute form but so mild in degree that it escapes recognition.

In all types, the involvement is diffuse throughout both lungs. The granular form presents a generalized stippled or "fine sandpaper" appearance suggestive of pulmonary edema, but closer inspection demonstrates that the changes are distinctly particulate in nature. There is usually no accompanying hilar node enlargement. In certain instances this granularity may serve as a background for a generalized reticulation, comprising the reticular form of Sosman and Wilson (29). In these there may be an accompanying slight to moderate enlargement of the hilar lymph nodes.

The nodular type, which is of primary concern in the differential diagnosis of silicosis, is characterized by the presence on the roentgenogram of evenly distributed nodular densities throughout the lungs. These vary from 1 or 2 to 4 or 5 mm. in diameter in different persons, but in a given case are generally uniform in size (Fig. 20). The tendency to coalescence is usually not well defined, although in some cases there may be a quite definite concentration of the nodulation in the upper lung fields (Fig. 21). The hila are frequently indistinct, and may be the site of a pronounced lymphadenopathy.

At the risk of digressing, a brief résumé of the symptoms and clinical course of this so recently recognized disease is offered. Dyspnea, cough, and weight loss, together with a long latent period varying from months to several years prior to onset, are cardinal features. A study of the ventilatory function in advanced cases reveals marked respiratory incapacity, which is in turn regularly accompanied by a secondary polycythemia. Hardy and Tabershaw (29) report a mortality rate of 35 per cent, but the outcome is not invariably fatal, and some of those cases which it has been our privilege to follow have remained relatively stationary over a period of several years, while others have shown varying degrees of improvement. Too short a time has elapsed to warrant final conclusions, and the ultimate result to be expected in the non-fatal cases is still a matter of conjecture. In any given case, however, attention should be directed to the fact that there is apt to be a striking lack of correlation between the clinical and the roentgen findings.

In autopsy material there is grossly apparent and diffuse thickening of the alveolar septa, usually most marked in the hilar portion of each lobe. Microscopically this is seen to have occurred secondary to a widespread cellular infiltration by macrophages and lymphocytes, with the associated formation of focal lesions in which there has been an obliteration of the alveolar spaces. Multinucleated giant cells of the Langhans' type are usually

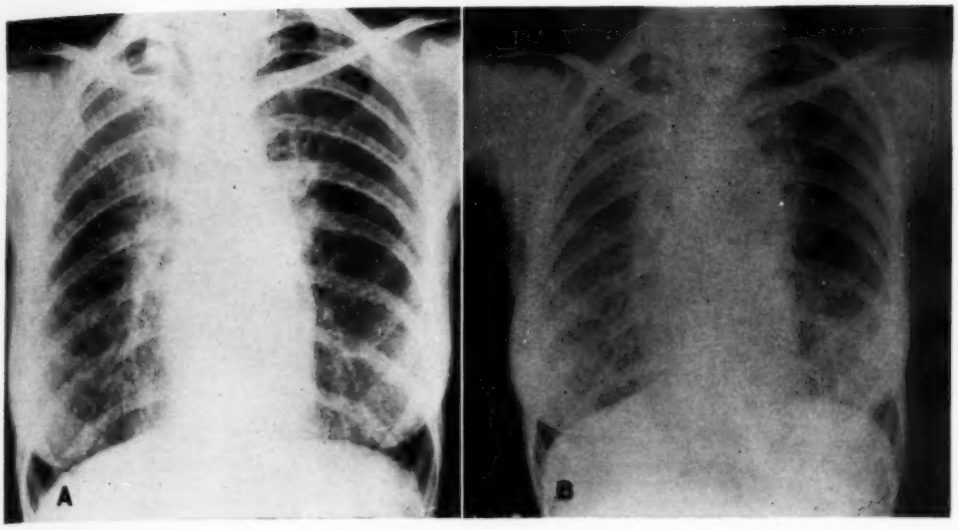

Fig. 21. L. M. Nodular type of chronic pulmonary granulomatosis occurring in a beryllium worker. A. March 3, 1944: Generalized nodulation with slight tendency to concentrate in upper lobes. B. April 18, 1945: Increasing tendency to "concentration" thirteen months later. Note the coexisting cor pulmonale.

demonstrable, and the irregular deposition of fibrous tissue within the lesions is a common occurrence.

As long as the granularity so characteristic of the granular and reticular forms of the disease persists, the differentiation of the various nodular pneumoconioses from chronic pulmonary granulomatosis of the type seen in beryllium workers does not present a difficult problem. In the nodular form, however, the roentgen appearance may simulate exactly that of silicosis and those benign pneumoconioses which exhibit a nodular predominance. In these cases recourse must again be taken to the occupational history and to consideration of the clinical and laboratory findings.

SUMMARY

(1) Attention is directed to the fact that a fluoroscopic and roentgenographic examination of the chest is the most precise method available for demonstrating in the living individual the pathological changes produced within the lungs by the pneumoconioses. The necessity, however, for correlating the roentgen findings with all other essential data before making a definite diagnosis is emphasized.

(2) "Pneumoconiosis" is defined as a broad generic term to include all forms of pulmonary reaction to dust lodging within the lungs. The rationale for further subdivision into the specific (silicosis and asbestosis) and non-specific or benign pneumoconioses, with a brief review of the etiology, pathology, and roentgen criteria for the diagnosis of each, is explored.

(3) The roentgen manifestations of simple silicosis and of silicosis complicated by the presence of coexisting infection, are detailed. The demonstration upon the roentgenogram of a generalized nodulation throughout the lungs is considered as fundamental to the diagnosis of silicosis.

(4) The differential diagnosis of silicosis and other conditions which may be productive of nodular densities within the lungs is reviewed.

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SUMARIO

Algunas Consideraciones sobre el Diagnóstico Roentgenológico de la Silicosis y los Estados que Pueden Simularla

Al llamar la atención sobre el hecho de que el examen roentgenoscópico y roentgenográfico del tórax constituye el método más preciso con que contemos para descubrir en el individuo vivo la patología intrapulmonar producida por las neumoconiosis, recálcase también la necesidad de correlacionar los hallazgos roentgenológicos con los demás datos esenciales antes de formular un diagnóstico positivo.

Defínese la neumoconiosis como amplio término genérico que comprende toda forma de reacción pulmonar al polvo que se aloja en los pulmones. Dos son las neumoconiosis específicas de importancia clínica: la silicosis y la asbestosis. Además, hay varias neumoconiosis banales debidas a la inhalación de polvos inertes pero opacos a los rayos X, cuya única importancia radica en la posibilidad de confundirlas con la silicosis.

Para el diagnóstico de la silicosis, es indispensable una historia de exposición adecuada a polvo que contenga bióxido da silicio. El típico cuadro roentgenológico de la silicosis simple consiste en nódulos discretos de tejido fibroso hialino esparcidos por todo el parénquima pulmonar. La silicosis acompañada de infección puede tomar la forma bien de tuberculo-silicosis o de silicosis con tuberculosis. La tuberculo-silicosis, que es una entidad patológica bien definida y diferenciándose tanto de la silicosis simple como de la tuberculosis, presenta un cuadro roentgenológico variado. En las etapas tempranas obsérvanse hebras lineales de fibrosis que acompañan a las nodulaciones. Más tarde, las últimas manifiestan concentración y coalescencia alrededor de los focos fibrosos, y pueden notarse típicas "sombras masivas," espesas y bien delineadas, de fibrosis conglomerada. La silicosis con tuberculosis toma dos formas. En una la infección tuberculosa se sobrepone a una silicosis evolutiva; en la otra las dos dolencias coexisten, pero actúan independientemente.

En el diagnóstico diferencial de la silicosis, hay que considerar los siguientes estados: baritosis; siderosis; neumoconiosis por talco; seudonodulación debida a inhalación de óxido estannoso; envenamiento por pentóxido de vanadio; tuberculosis; histoplasmosis; algunas de las micosis; hemosiderosis pulmonar; policitemia vera; metástasis carcinomatosas; sarcoide de Boeck, y granulomatosis pulmonar crónica en trabajadores en berilio.

Significance of Occupational History in Diagnosis of Silicosis[1]

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SINCE THE PULMONARY changes of early silicosis, as revealed by chest roentgenograms, are not characteristic of that disease alone, an occupational history is emphasized by radiologists as an essential aid in diagnosis. That is to say, there must be confirming evidence of sufficient exposure to a known silicosis-producing dust before a diagnosis of silicosis is permitted. Thus, an adequate occupational history is required as much as are chest films of high quality, and proper interpretation of the essential facts of the history becomes quite as important diagnostically as skillful reading of the films.

The implication of the foregoing is clear, namely, that the etiology of silicosis is so well understood that, in one case, it can be said that the history provides confirming evidence of a silicosis hazard, whereas in another, it does not. The purpose here is to review the evidence upon which our present knowledge of the etiology is based and to consider the limitations of this knowledge as well as the extent to which it can be applied in the interpretation of occupational history.

It must be understood at the outset that there is nothing inherent in an occupational history which proves by itself that a silicosis hazard does or does not exist. A certain type of dust exposure is now recognized as hazardous only because it was previously shown by independent diagnosis that silicosis developed in a significant number of men thus exposed. An adequate occupational history, then, is one which shows that the dust exposure has (or has not) been similar in essential detail to exposures previously found to be hazardous. The problem is not difficult when the record includes evidence of prolonged exposures in occupations known to be dangerous, such as dry-drilling in a hard rock mine or granite cutting without dust control. Difficulties arise when the exposure has been to a dust and in an occupation about which little is known. Here we must depend upon analogy. Is the dust, in fact, similar to another of known hazard, despite some obvious differences, and are the conditions of exposure, when reduced to basic etiological factors, like those found in occupations of recognized hazard? The certainty with which these questions can be answered depends upon another question: Are the essential etiological factors which we now accept and use in appraisal of dust hazards so basic and universal that they apply with equal significance and exclusively to all dusts, regardless of differences in respect to other conditions of exposure?

ETIOLOGY OF SILICOSIS

The basic framework of our present understanding of the etiology of silicosis comes largely from a series of systematic studies in a few industries with which silicosis is historically associated; that is, industries in which the hazard was so great that the disease was common among the workers and recognized by them (stonecutter's consumption, miner's phthisis, potter's rot, etc.). These studies established certain basic relationships between the occurrence and incidence of silicosis and some pertinent facts of dust exposure, which may be summarized, as follows:

1. Silicosis is caused by the specific action upon lung tissue of silicon dioxide (SiO_2) in the free state, which has accumulated in the lungs as a result of prolonged exposure to this compound as finely divided, air-borne dust.

2. Translated into quantitative terms,

[1] Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

the studies show that the magnitude of the hazard increases with: (*a*) percentage of free silica in the air-borne dust; (*b*) dust concentration; (*c*) years of exposure. The size of the dust particles was also shown to be significant, in that particles must be small enough to penetrate to the alveoli upon inhalation.

3. Of great practical importance is the conclusion from all these studies that silica must accumulate in the lungs in sufficient quantity before silicosis develops and that, below certain levels of concentration, the hazard is negligible, even for prolonged exposure. Thus, maximum acceptable concentrations were proposed for the industries studied, below which no significant hazard is presumed to exist.

Generalizing from these basic findings, it has become common practice to appraise the silicosis hazard in dusty occupations by quantitative measurements to determine (*a*) the percentage of free silica in the dust and (*b*) the dust concentration, and to compare the findings with standards of permissible dustiness. Generalizing to the extreme, the following practical rule has been proposed: multiply the percentage of free silica by the dust concentration; if the product is below five million particles per cubic foot, then a silicosis hazard is presumed not to exist. This rule assumes that the hazard is directly proportional to the concentration of silica in the dust and that a concentration of five million represents the upper limit of tolerance. The rule does not apply when the silica content is below 5 per cent.

One may not agree that the evidence justifies so precise a formula as the above, but that does not deny the significant implication, namely that our present view of the etiology of silicosis is based upon a *quantitative* concept—that a silicosis hazard exists only where there has been exposure to a sufficient amount of silica dust of the proper particle size over a long enough period of time. An occupational history which merely records, chronologically, the industries in which the man has worked and the kinds of jobs performed provides very little meaningful information. More detailed data are required to assess the actual dust exposure in quantitative terms. Even when the record includes work in a dusty trade of known hazard, further detail is required. To illustrate: all pottery workers are not exposed to silica dust (*e.g.* decorators); the dust hazard varies widely within foundries; in an anthracite coal mine the silica exposure for the hard-rock miners is quite different from that of the coal miners, and in a bituminous coal mine the principal silica exposure is from the traction sand used on the locomotives rather than in the mining operations; even sand blasting may not be significant today since, with modern protective equipment, there is little exposure to silica dust.

It is to be noted that the studies upon which the foregoing relationships are based were limited to a few industries in which silicosis was, in the past, a characteristic disease. Recognizing this, it was emphasized in each case that the findings and conclusions pertained only to the particular industry studied and should be applied to others with caution.[2] The etiological factors which were identified are undoubtedly basic but they are not necessarily the only ones, and in other occupations and industries the hazard may be modified or intensified by the influence of forces not present or recognized in the original studies.

Laboratory investigations have largely confirmed the basic findings of the systematic industrial studies but they have also shown that other factors, not included in the general summary presented above, are of etiological importance. Some of these are considered below.

Dust Composition: The specific action of the free compound, silicon dioxide, has been confirmed in the laboratory. Free silica exists in several different forms: amorphous as well as crystalline, and in different

[2] Even within these industries, limitations were recognized because it was not possible to determine, with finality, the magnitude of past dust exposure, owing to inevitable changes in processes and operations and success of dust control. Certain assumptions had, therefore, to be made to relate dust concentrations, as measured, to past exposures.

crystalline patterns. All possess the unique tissue-damaging capacity, although to different degrees. Other substances mixed with free silica may possess the power to enhance or reduce the activity of the silica. Some apparently serve as protective agents. Clay dust, for example, containing some free silica, apparently does not have the same hygienic significance as an equal amount of free silica alone.

The demonstrated capacity of certain types of dusts, like iron oxide, to produce x-ray shadows simulating silicosis further complicates the problem. With a complex dust containing both silica and a radiopaque material, what weight is to be given to each in appraisal of the dust hazard and interpretation of lung markings?

In view of these observations, a simple determination of the free silica content may be incomplete as an index of hazard in the case of a complex dust exposure.

Particle Size: The use of atmospheric dust concentration measurements to provide an index of dust accumulation in the lungs is justified only on the assumption that there is an approximately constant fraction of the inhaled dust which comes to rest in the lung depths. Particle size is of direct influence, however, in determining the amount of dust which penetrates to and is retained in the alveoli. Within the normal range of sizes of particles encountered in typical industrial dusts, there is wide variation in the percentage which is retained in the alveoli. Thus, for equal atmospheric concentrations, two dusts of different particle size may behave quite differently in respect to lung deposition. Varying degrees of flocculation or aggregation of fine dust particles which occur in industrial dusts also cause differences in the percentage of inhaled particles which penetrate to the lung depths.

Particle size is of further interest even after the dust has reached the lungs. Laboratory studies have shown that is has marked influence upon the rapidity and amount of tissue damage produced, and the differences are of such magnitude that they may overshadow other factors in an experiment unless size is carefully controlled.

Although particle size is listed among the basic etiologic factors, it is not commonly considered in standard appraisal work beyond demonstrating that the size range is not unusual. The foregoing suggests that it may be a major factor, requiring more extensive evaluation in the appraisal of dust exposures.

Composition in Relation to Particle Size: Since the coarser dust particles, 5 to 10 microns and more, are largely removed in the upper respiratory tract and are essentially inactive in lung tissue, even if they do penetrate to the alveoli, it is evident that the percentage of free silica in this larger size range has little influence upon the silicosis hazard of a given dust. On the other hand, the greater portion of the total weight in a dust sample is contributed by these large particles, the composition of which will, therefore, largely determine the analysis of a given sample. It has been shown that the free silica content varies considerably with particle size in many complex industrial dusts. An outstanding illustration is foundry dust, which generally has a high free silica content in the coarser particles (5 to 10 microns and larger) but a relatively low percentage in the fraction smaller than 5 microns, which more closely represents the particles which are deposited in the alveoli. Even more striking are the findings in a plant crushing and grinding sandstone. Although the parent material contained 95 per cent quartz, the free silica content of the dust smaller than 5 microns varied within the plant from more than 90 per cent down to as low as 24 per cent.

A dust in which the free silica is largely accounted for by coarse particles does not possess a silicosis-producing capacity equal to that of another dust of equal silica content in which, however, the silica is concentrated in the fine dust. It is evident that a meaningful determination of the free silica content of industrial dusts must take into account the variation in composition with particle size. For example, super-

ficial dust appraisal of foundries indicates that the percentage of free silica and the dust concentration have been as high in the past as in granite cutting shops, if not higher. A comparable incidence of disabling silicosis, however, has not been demonstrated.

Dust Concentration: The present assumption of a directly proportional relation between dust concentration and magnitude of hazard is logical and has provided a useful guide in the statistical analysis of the findings of the systematic studies of silicosis. There has been no quantitative study, however, of the effect of intermittent high concentrations, the so-called "dust floods." Does a concentration of 200 million particles per cubic foot of air for a period of one-half hour, for example, have the same significance as the same total intake spread over eight hours, that is, with a concentration of 12 to 13 M.P.C.F.? Physiological considerations suggest that the two are not equivalent. In the industries in which silicosis has been a characteristic disease, the exposed workers were subject to a fairly constant and intimate dust load over many years. A systematic relationship between dustiness and years of exposure and incidence of silicosis is, therefore, more to be expected than in an industry or occupation where dust exposure is intermittent.

SUMMARY

It is not the purpose here to minimize the significance and value of present methods of appraising dust exposures but, rather, to call attention to some factors which are not commonly taken into consideration and which may limit the application of present criteria. So long as the roentgenologist demands the added evidence of the occupational history to assist in the diagnosis of non-specific x-ray findings, it is essential that these limitations be recognized. The danger inherent in short-cut methods of assessing dust hazards was especially emphasized by Dr. Leroy Gardner in his well-known paper on "Etiology of Pneumoconiosis."

The dusty trades may be divided into three categories in respect to silicosis: (1) known to produce silicosis as a characteristic disease of the occupation; (2) known to be free from the silicosis hazard because of the certain absence of silica dust exposure; (3) intermediate industries and occupations in which silicosis occurs sporadically. Meaningful interpretation of occupational history is not difficult in the first, provided it includes sufficient detailed information pertaining to the amount of silica dust and duration of exposure. The second category presents no problem, since silicosis is ruled out automatically, provided mineralogical analysis of the dust has shown that free silica is not present. In the third group, however, the detailed information of the occupational history is of greatest importance, and the adequacy of our present etiological criteria of greatest concern. There is danger in applying the generalized rules too far in the evaluation of dust exposures for the purpose of diagnosis of individual chest roentgenograms. Further laboratory research is needed to improve our understanding of the etiology of silicosis and thus increase the certainty with which occupational histories can be interpreted. It is of even greater importance, however, that the independent reading of chest roentgenograms be extended without dependence upon occupational histories.

More systematic studies of the type described above are needed in a greater variety of dusty trades, involving exposures to more complex dusts and including, in particular, occupations in which silicosis is an occasional rather than a characteristic occupational disease; others, in which non-disabling lung changes occur, such as in welders, also require systematic study. The statistical aspect of the problem must be kept in mind. A chest film which is non-specific when viewed alone takes on new meaning when it is found to be characteristic of a group of workers similarly exposed. Further confusion with respect to the true distribution and magnitude of the silicosis hazard in industry can be

avoided only by the most critical study of the findings in the borderline dusty trades. The responsibility is a joint one, shared by radiologists, clinicians, pathologists, and industrial hygienists.

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SUMARIO

Importancia de la Historia Profesional en el Diagnóstico de la Silicosis

Los oficios polvosos pueden ser divididos en tres categorías con respecto a la silicosis: (1) los que reconocidamente provocan silicosis como típica enfermedad profesional; (2) los reconocidamente exentos del riesgo de silicosis por la falta positiva de exposición al polvo de sílice; (3) las industrias y oficios intermedios en los que ocurre silicosis esporádicamente. La interpretación acertada de la historia profesional no resulta difícil en el primer grupo, con tal que haya a mano suficientes pormenores en cuanto a la cantidad de polvo de sílice y la duración de la exposición. La segunda categoría no entraña problema alguno, pues la silicosis queda excluída automáticamente. En el tercer grupo la historia profesional es muy importante y las pautas etiológicas revisten la mayor trascendencia.

En todo estudio etiológico de la silicosis, los factores que hay que tomar en cuenta son: la composición del polvo; el tamaño de las partículas, que ayuda directamente a determinar la cantidad de polvo que llega a los alvéolos y es retenida en los mismos; la composición del polvo en relación con el tamaño de las partículas; y la concentración del polvo. Necesítanse más estudios de laboratorio para perfeccionar nuestra comprensión de estos y otros problemas y acrecentar así el acierto con que se interpretan las historias profesionales. Todavía es más importante que se extienda la lectura independiente de las radiografías torácicas sin sujeción a la historia profesional. También hay que tener presente el aspecto estadístico del problema. Una radiografía del tórax que parece atípica al ser estudiada por sí sola cobra nuevo significado al descubrirse que es característica para un grupo de obreros expuestos en forma semejante.

Anthraco-Silicosis[1]

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THE TERM "anthraco-silicosis" is a descriptive title for the form of pneumoconiosis commonly called "miner's asthma." It is a chronic disease due to breathing air containing dust generated in the various processes involved in the mining and preparation of anthracite coal. It is characterized anatomically by generalized fibrotic changes throughout both lungs with the presence of excessive amounts of carbonaceous and siliceous material, usually by compensating emphysema, and often by cardiac changes in the later stages of the disease.

The purpose of this paper is to present a review of some observations made in coal miners with anthraco-silicosis in the anthracite coal fields over a period of twenty-seven years. We will not go into detail as to pathogenesis, as this is discussed elsewhere in this symposium. The presence of the silica particles in a certain concentration, their size, and the changes that ensue in the lungs after they are deposited there are well known to most of you.

We have had an opportunity to observe this disease in coal miners during many years. When we were in general practice, most of our male patients were coal miners, and in the years devoted to roentgenology we have personally studied approximately a thousand cases a year for twenty-five years. About fifteen years ago, in association with the late Dr. Byron H. Jackson, we studied one thousand cases from the standpoint of the age and build of the worker, the working conditions, years of exposure, and race. We found no resistance to the disease on the part of any particular race. It was our experience that when a man was exposed to a silica hazard, it took from five to seven years before there were any distinctive changes in the lungs that could be noted on the roentgenogram. This, of course, was in the average case. It is universally conceded that the only way that the diagnosis can be made in the living is by roentgen examination.

We believe, however, that a diagnosis of first-stage anthraco-silicosis cannot be made with any degree of assurance on the roentgenogram alone. The history must be obtained. This is not true concerning the second and third stages of the disease. Their roentgenographic appearances are characteristic and the diagnosis can be made with less consideration of the history.

During the past several years, we have been associated, in a minor way, with Dr. Lewis Gregory Cole in the study of silicosis. Preliminary reports have already been made and we are anxious to know his final conclusions.

One of the most brilliant contributions to American radiology, on the subject of silicosis, was made by the Chairman of this Symposium, Dr. Eugene P. Pendergrass, and his illustrious chief and predecessor, the late Dr. Henry K. Pancoast. No study of this subject can be complete without a review of their work. One of the first papers on this subject in America was contributed by Childs, in 1917, to Lanza's "Miners' Consumption." Three stages were described as shown on the roentgenogram. This classification is very good and has stood the test of time. In 1916, Watt, Irvine, Johnson, and Steuart described three pathological stages: early, intermediate, and advanced silicosis. Many others have contributed to our knowledge of this subject. The list is too long to mention, but we find quite frequently in the literature such names as

[1] Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

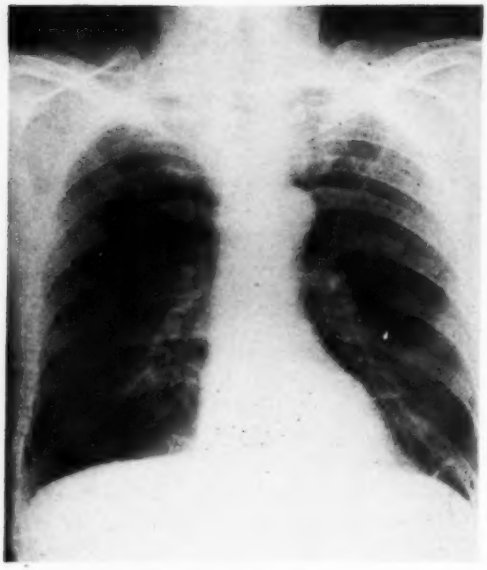

Fig. 1. Bilateral peribronchial perivascular fibrosis. First-stage silicosis.

Gardner, Drinker, Sayers, Sampson, Judd, Riddell, and Hoffman.

We cannot emphasize too strongly the necessity of a very thorough roentgen examination of the patient's chest. We believe that fluoroscopy is a most valuable aid in this condition and that it has been too much neglected. This part of the examination gives us information about the ventilation of the lungs and the movements of the diaphragm that we cannot obtain by any other method. Stereoscopic roentgenograms made in inspiration and expiration are indispensable in the first and second stages of anthraco-silicosis.

We do not often encounter infection in either lung in the first two stages of this disease. It is in the third stage that infection occurs more frequently. Non-specific infection in either or both lungs in the first and second stages responds quite well to ordinary treatment. This is not true when the infection occurs in the third stage, and it is our opinion that it is infection, superimposed upon the anthraco-silicosis, that is the principal cause of the disability.

It is amazing to see how men do laborious work every day with advanced silicosis, apparently without complaining of symptoms if they are present. These are usually cough, some dyspnea and tightness in the chest, and sometimes pain. It has been our experience that tuberculosis is not a common complication of anthraco-silicosis in the first two stages and under the age of fifty. After the age of fifty, and usually in the third stage, tuberculosis is more common in silicotic individuals than in those not so affected.

According to the laws of the State of Pennsylvania, active tuberculosis is the only complication of anthraco-silicosis allowed in a disability claim. When a worker claims total and permanent disability from anthraco-silicosis it must be due to that condition alone, with the single exception just mentioned.

Anthraco-silicosis is a progressive, incurable disease. At this point the question may arise as to its rate of progression when the worker is removed from the silica hazard. The answer depends on the stage of the disease at the time of removal from exposure. In the first two stages, the disease progresses slowly. We have never known of a case where a first-stage anthraco-silicosis progressed to a third stage when the patient was completely removed from the hazard. Theoretically, the condition should keep on progressing as long as the patient lives, and this may happen in some instances, but we have never observed it. Cases in the late second and beginning third stage will continue to progress even after exposure has ceased, but not so rapidly as if the patient remains in the irritating atmosphere. This seems reasonable. We have known of many individuals who were exposed to a silica hazard for periods of eight to ten years, whose roentgenograms showed a first-stage anthraco-silicosis that did not progress beyond a middle second stage. We believe that roentgen studies of the chest should be made in such persons as long as they live in order that this question may be answered more definitely.

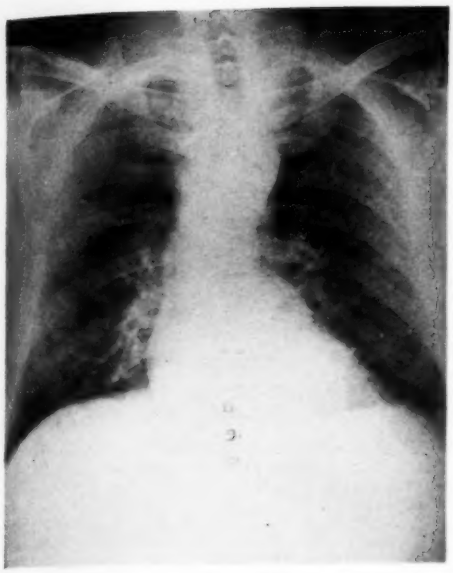

Fig. 2. Bilateral discrete nodulation. Second-stage silicosis.

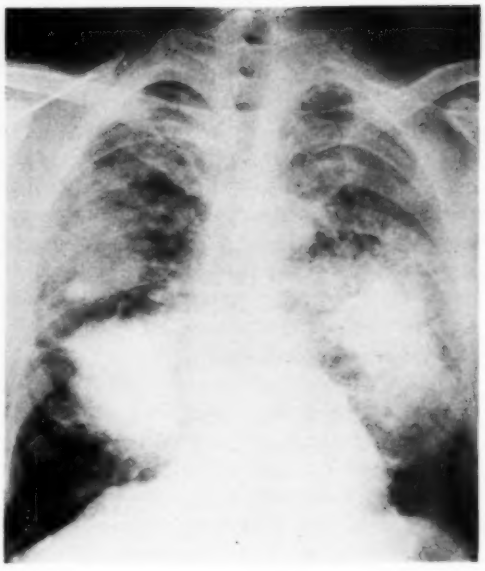

Fig. 3. Bilateral diffuse nodulation with large conglomerate masses. Third-stage silicosis.

In the State of Pennsylvania, at the present time, workers with anthraco-silicosis are appearing in the compensation courts, claiming total and permanent disability. In order to obtain a hearing, they must prove that they have worked in a silica hazard for four out of the eight years immediately preceding the date of disability. To establish the existence of a hazard, the attorney usually asks whether the seams of coal in the mine in which the claimant worked were underlaid and overlaid with sand rock. The answer is always "Yes."

No one questions that anthraco-silicosis exerts an effect on the worker, but it is our opinion that a total and permanent disability resulting from anthraco-silicosis alone is not very common. We have never observed an instance of total and permanent disability from anthraco-silicosis alone unless the disease had advanced well into the third stage.

In determining disability the heart is of major interest. It is not easy, however, to determine whether cardiac disease results directly from anthraco-silicosis when the patient is at an age when cardiovascular and renal diseases are usual. Right heart hypertrophy can be shown to exist only by demonstration of increased thickness of the wall of the right ventricle when that of the left ventricle is normal. We feel that one cannot faithfully contend that there is not right heart strain when both lungs are the site of considerable fibrosis, collagenous material, infection, and emphysema.

The degree of disability of a person with anthraco-silicosis should, in our opinion, be decided by a small group consisting of an experienced roentgenologist, a clinician, and one or two laymen, all of whom are acquainted with the working conditions in the anthracite coal mines. It would be helpful, of course, if one of this group were also learned in the law.

Since anthraco-silicosis is a progressive, incurable disease, there is only one way to counteract it, and that is to remove the silica hazard from the atmosphere in which the man works. We cannot remove the man without closing the industry.

We have investigated the action of aluminum in counteracting the deleterious effects of silica. Conclusions differ as to

its effectiveness. We have heard of some good results obtained in Canadian mines. The procedure is to bring about a concentration of aluminum dust in the wash rooms and the rooms where the men change their clothing before and after work. This is accomplished by having the aluminum blown through pipes with compressed air in an air-tight room. According to reports coming from Canada, the silicosis progresses more slowly and years have been added to the lives of the workers.

In our conversations with the mining men and workers in the anthracite field, we have found them of the opinion that the best practical way to remove the silica hazard is by a system of water sprays, spraying water over the face of the chamber before and after drilling and blasting. There is also a mechanism provided whereby water is pumped into the hole when the drill is in operation, thereby keeping down the dust with its contained silica. In addition to the above, there should be the best possible ventilation.

There are many places in the anthracite coal regions where this water method is now in operation and it is very effective. The use of masks, in our opinion, would also be beneficial, but the men are not enthusiastic about this suggestion. The coal industry is doing all it can to reduce the hazard at the present time. More could have been done in the past.

Recently a large sum of money has been donated to one of the leading hospitals in Philadelphia for research and treatment of persons with anthraco-silicosis. This work was started a short time ago and, so far as we know, no report concerning results or conclusions has yet appeared.

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SUMARIO

Antracosilicosis

La antracosilicosis es una forma de neumoconiosis observada en los mineros de antracita, caracterizándose por fibrosis generalizada en los pulmones, con existencia de cantidades excesivas de sustancias carbonáceas y silíceas, habitualmente por enfisema de compensación, y a menudo, en sus últimas etapas, por alteraciones cardíacas.

En el primer período, el diagnóstico no puede basarse exclusivamente en la radiografía, pero en el segundo y el tercer períodos el cuadro roentgenológico es típico. El examen debe comprender la roentgenoscopia, que aporta datos importantes en cuanto a la ventilación de los pulmones y los movimientos del diafragma, y películas estereoscópicas obtenidas en la expiración y la inspiración.

En el primer y segundo períodos de la antracosilicosis, la infección no reviste mucha importancia, pero en el tercer período pasa por ser la principal causa de incapacidad.

La enfermedad es evolutiva e incurable, pero el alejamiento de la atmósfera polvosa retarda la agravación. La prevención se basa en la eliminación del riesgo inherente al silicio. La pulverización con agua de los filones de carbón antes y después de taladrar y explotar ha resultado eficaz en dicho sentido.

Pathogenesis of Industrial Pulmonary Disease[1]

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THE BROAD TERM, industrial disease, implies disease of occupational origin and includes disease or injury from physical agents, such as mechanical force, heat, cold, radiation, pressure, etc., as well as the infections and allergic diseases. For purposes of this discussion, however, we limit the field to subacute and chronic diseases of the lung resulting from agents in particulate state and of sufficiently low solubility to be capable of producing chronic rather than acute disease. This limitation excludes the highly soluble chemical irritants, gases, vapors, and agents of this class adsorbed upon inert particulate matter, since the effects of the adsorbed agent are like those of the free agent after entry into the lung.

For purposes of definition, we exclude from consideration the large number of lung alterations caused by inert dusts, identifiable by x-ray and associated with minimal pathologic changes, but not resulting in clinically evident disability during the ordinary life span. In addition, we may exclude the changes caused by the salts of iron, silver, tin, barium, and the like, which produce striking changes in the roentgenogram, but which are not usually associated with functional disturbance. These latter states, like the so-called benign pneumoconioses, in all probability do cause local changes but require so long for evolution as to be relatively benign during the lifetime of the individual.

PATHOLOGICAL PHYSIOLOGY

The preceding paper has clearly defined the qualitative and quantitative elements that must enter into an evaluation of significant exposure. The lung itself has an important role, since the occurrence of pathologic changes may be influenced by a number of variables operating within it. In the normal course of events following the inhalation of a noxious dust, the dust particles are picked up by the phagocytes and/or the mobile septal cells which have taken over phagocytic function. These enter the lymphatics and migrate toward the hilar nodes and pleura, thence in part by way of the thoracic duct to the general circulation. Animal experiments have demonstrated that, following exposure to willemite, dust-laden phagocytes may appear in the hilar nodes in from twenty to thirty minutes after the beginning of exposure. Large numbers may perish on the way, however, resulting in local accumulations of dust in the periphery; and, of course, peripheral accumulations will be prominent if the mass of incoming dust exceeds the drainage capacities of the lung. In the case of irritant and chemically active dusts, this rate of removal is also delayed because of the direct effect of the dust upon the phagocytes and because of changes in ventilation which occur.

The inhalation of irritant dusts results in certain changes in the behavior of the lung, which in the case of some of the more active dusts tend to create conditions which favor the retention of the very fine particles in larger numbers than would be expected to occur on a theoretical basis alone. The character of this response is shown in Figure 1, which illustrates a series of closed circuit experiments using broncho-dilating agents and irritant dusts.[2] The curve is so laid out that a depression in base line represents a reduction in lung volume; and a rise, an increase. The excursions relate directly to the amplitude; the rate is measured by the frequency per unit time.

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[1] Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston Mass., Nov. 30–Dec. 5, 1947.

[2] This figure was kindly loaned by Professor Lucien Dautrebande.

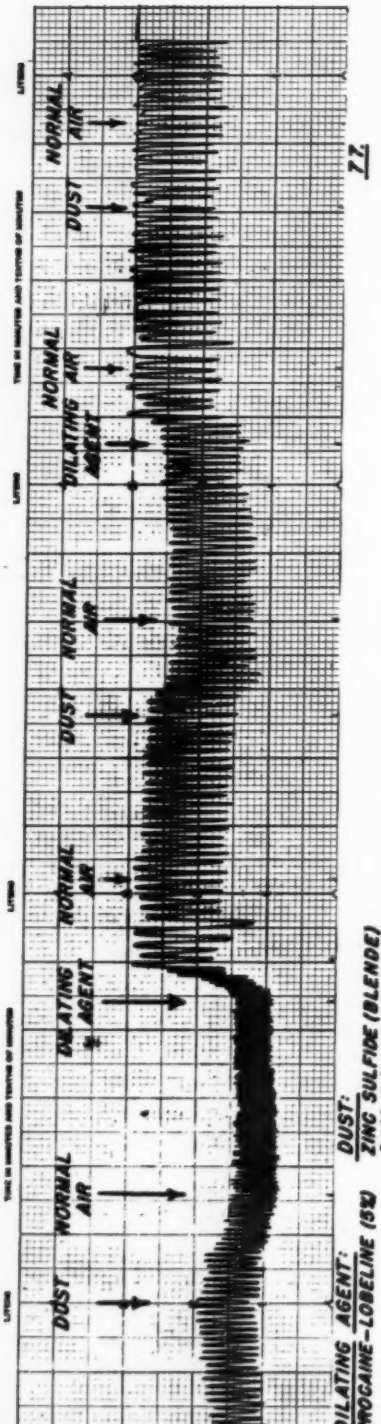

Fig. 1. Effects of inhalation of irritant dusts.

It can be seen that, following even a very short period of inhalation of irritant dust, there is a reduction of about a half liter in pulmonary volume and a great increase in rate. This is a change associated with bronchiolar constriction, which, if maintained, leads to stasis of secretions, patchy atelectasis, and emphysema (a type of change which in fact is characteristic of pneumoconioses).

It can further be seen from Figure 1 that the inhalation of agents which will dilate the bronchioles will cause a return to normal function and an increase, in this case of almost a liter, in lung capacity.

Bronchiolar constriction is associated with an increase in residual air with large numbers of alveoli atelectatic and others dilated and emphysematous. In the normal individual we assume practically zero velocity for air movement within the alveoli. Be that as it may, in any situation such as the above, with the trapping of large quantities of air, optimal circumstances are set up for the retention of particles. Because in atelectatic areas there is reduction in capillary flow (and probably in lymphatic flow as well) as a result of the local collapse, this response also creates conditions favoring accumulation of phagocytes which have already engulfed dust. Since the taking up of particles by phagocytes does not destroy the toxic and proliferative properties of the materials, and since, as we also know, phagocytes may die *in situ*, autolyze, and liberate dust which may then stimulate local fibrosis or perhaps be picked up again by other phagocytes, it follows that the atelectasis and emphysema resulting from bronchiolar constriction favor markedly the local deposition of dust.

The great majority of particles are carried by way of the lymphatics to the hilar nodes, as described. A number, however, find their way directly into capillary and venous channels and enter the systemic circulation. This double drainage system constitutes a protective mechanism when dealing with particles that have settled in the alveoli. Obviously the behavior of the

lung as it affects the over-all drainage rate is a very important consideration in the pathogenesis and type of onset of disease. Pathological studies of local deposits in the lungs almost uniformly show that the upper portions are first and most severely affected, while the diaphragmatic surfaces are largely free. This strongly suggests that the rate of drainage and removal of particles is closely related to lung movement and is consistent with the observation that continued activity at times delays onset and may lessen disability in some progressive pulmonary diseases. A further point in more recent studies of pulmonary granulomatosis in beryllium workers is consistent with this hypothesis, the onset of clinical illness in a number of these cases being associated with intercurrent infection, pregnancy, and the like, all of which tend to reduce normal respiratory movements and limit activity.

CHEMICAL CONSIDERATIONS

The earlier concept that the production of pneumoconiosis was a result of physical characteristics, principally sharpness of particles, has fallen into disrepute. At the present time, one leans to the hypothesis that solubility of the particle or leaching of specific ions is the responsible agency. Before one accepts this hypothesis, however, certain critical considerations must be dealt with. For one, if the dissolution of the particle with the liberation of irritant material is responsible, then a systematic classification of materials of similar chemical structure and irritant capacities should be possible upon some rational basis. We are nonetheless forced to say at present that the difference between active and inactive dusts has not yet been defined on other than an empirical basis. The chemical attributes of inhaled material must affect profoundly the character and degree of tissue reaction. We know that the inert dusts, such as marble, carbon, calcium carbonate, etc., have little capacity for stimulating proliferation of fibrous tissues and multiplication of phagocytes, while others, such as silica and beryllium, will do so. This property of chemotactic activity may occur not only with inorganic compounds but also with organic, as in the case of the waxy coat of the tubercle bacillus. We have, regrettably, no method to measure this capacity other than by testing with experimental animals.

Any chemical theory of pathogenesis of pneumoconioses must account for varying effects of solubility in dealing with dusts of like chemical nature. Thus, forms of silica, which will vary in their physical structure, must be shown to have different rates of solubility, or capacities to form compounds which are unlike, in order to explain the variations shown to exist in their individual capacities to produce disease. Toxic materials and ions, therefore, which dissolve from surface, must be quantitatively and qualitatively shown to leach or dissolve in different orders of magnitude, and these orders then be related to pathogenesis. In the case of silica, this in general has been shown to be true. King (1) has demonstrated, for example, that quartz and flint, which are among the most toxic of dusts, dissolve to the extent of about 10 mg. silica/100 ml. of plasma, while the less pathogenic dusts, such as shale and mica, dissolve only to the extent of 1 to 2 mg./100 ml. of plasma.

A similar relationship is being developed for certain compounds of beryllium, in that the rate and equilibrium solubility of certain lamp phosphors which are suspected of causing disease have been found to be several-fold that of others which have not yet been indicted as pathogenic.

There must be, moreover, an optimum range of solubility for production of chronic disease. The determination of solubility of silicious materials offers numerous technical difficulties. There are apparently many degrees of freedom in the relationship, since the amounts which go into solution are influenced by the total amount present, by the surface, and by other solutes in the systems. Colloidal solutions tend to form, so that many factors undoubtedly enter into the relationships in the tissues where ion exchange itself may

be an important variable. King (1) and others, in their definitive investigations of the solubility theory of silicosis, have demonstrated that solubility of quartz dust is inversely related to the particle size and have shown, moreover, that a progressive diminution of solubility, without regard to size, takes place after repeated extraction with Ringer's solution. While this phenomenon will offer an explanation for the limited extension of the silicotic process after removal from exposure, it will not aid in understanding the latency of disease which, for example, is associated with exposure to beryllium compounds. The critical characteristic of solubility rate in determining *kind* of effect has now been shown by studies of several groups. Silica particles of moderate size range (0.5–3.0 microns) will produce characteristic pathologic changes whether inhaled or injected. Extremely fine particles, however, while apparently capable of producing early death, will not cause the characteristic tissue reaction with fibrosis and nodulation. This can be explained on the basis of the high solubility rate resulting from the vastly greater surface of the smaller particles.

Again, the studies of Chapman (2) and others on so-called acute silicosis have demonstrated that very rapidly developing silicosis may occur when the silica is mixed with an alkaline medium, and silica has been demonstrated to be more soluble in alkaline solution.

Other unsolved problems not yet explained by the chemical theory are those of the effects of critical concentration and its relation to rate and course of development of disease. Silica is extremely widespread, and significant amounts of mixed dust are breathed daily by all of us. It is obvious that either there must be a critical concentration for development of proliferative lesions or that the rate of proliferation caused by small orders of stimulus is sufficiently low to be of no practical significance in a lifetime. No entirely satisfactory chemical theory can be considered tenable until all of these phenomena are accounted for.

PATHOGENESIS

It follows that the development of chronic pulmonary disease of the type under consideration is dependent upon the following conditions: (*a*) a chemical characteristic of the dust; (*b*) a solubility rate of particles within certain ranges; (*c*) adequate concentration of dust exposure maintained for a sufficient period of time. The rate of development will be influenced also by the adequacy of the drainage system as determined by the previous history of the lung with respect to infections and exposure to the specific irritant.

The process by which the phagocytes and the wandering septal cells come out into the alveoli and carry off the particulate matter has been well described by Gardner, Cole, Policard (3, 4, 5), and others. Like the dead on the battlefield, the distribution of phagocytes and pathologic lesions portrays the tide and movement of this battle. Tissue reactions are seen peribronchially, in the pleura, in the perivascular tissues, along the lymphatics, in the interstitial tissues, in the alveolar walls, and elsewhere. The localization of the irritant is evident from the histopathology; and where phagocytes have accumulated and died, focal proliferation occurs.

This proliferation of fibrous tissue in the perilymphatic sheaths and the often massive accumulation of phagocytes impede lymphatic drainage, allow more time for action of the dissolving dust upon the phagocyte, and further hinder the normal cleansing process carried out through the lymphatics. Additional dust or dissolved material then piles up in increasing amounts.

In connection with the migration of particles, it is important to keep in mind that, while the outstanding pathology may be within the lung and the disturbance of lung function may dominate the picture, all of this class of diseases are potentially, and perhaps always, to some degree, general diseases. The migration of phagocytes and the dispersion of particulate matter throughout the organism does not remove

the offending agent from the body—this can come about only by solution and excretion. The lung is the repository and is generally most affected. Nonetheless, with long continued severe exposures, other lesions regularly develop in the abdominal viscera, especially the liver and spleen. While no pathologic involvement of the kidney has been reported, large numbers of particles may be seen throughout the kidney tissue, especially in the glomerular tufts. An organ high in reticulo-endothelium but very little studied is the bone marrow. In view of studies with a number of colloidal compounds, one would anticipate considerable accumulation in the marrow and bone.

PATHOLOGY

What one finds by way of gross or microscopic pathology depends primarily, of course, upon the dust, but will be influenced markedly by other variables. The lung as a group of tissues in the body, is capable of only a limited number of kinds of reaction. As the pioneering work of Gardner has shown, silica can cause every type of cellular reaction found in tuberculosis. In view of the difficulties of all pathologists in differentiating proliferative and granulomatous lesions, it is not astonishing that this should occur with similar types of change in the human lung. Without knowledge of exposure, it would be extremely difficult, if indeed possible in every case, to differentiate a whole family of pathologic lesions—some infectious, some chemical in origin. When the over-all architecture of the pathology in the lung is typical for the kind of exposure, the interpretation of the pathology is not too difficult. As our knowledge of the pneumoconioses widens, it becomes more apparent that the atypical lesions are increasingly common, as borne out by the recent studies on tremolite talc, diatomaceous earth, aluminum and silica abrasives, graphite, mica, beryllium, etc.

In light of the above, it is to be anticipated that the roentgen differentiation of lesions will be difficult, as indeed it is.

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SUMARIO

Patogenia de la Neumopatía Industrial

La inhalación de polvos irritantes da por resultado ciertas alteraciones en el comportamiento del pulmón. Aun después de un breve período de exposición, hay disminución del volumen pulmonar en presencia de constricción bronquiolar, y si se mantiene ésta, conduce a atelectasia y enfisema, las cuales, a su vez, favorecen el depósito local de polvo. Toda obstrucción del mecanismo eliminador del pulmón, que normalmente actúa como sistema protector para atender a las partículas depositadas en los alvéolos, es un factor contribuyente a la patogenia.

El antiguo concepto de que la producción de neumoconiosis dependía de las características fisicas de los polvos, ha sido suplantado por la doctrina de que la aparición de la enfermedad se enlaza más bien con las características químicas y el índice de solubilidad de las partículas inhaladas dentro de ciertos límites. La concentración adecuada del polvo y el mantenimiento de la exposición durante un período de tiempo suficiente son indispensables, y la evolución se verá además afectada por la suficiencia del mecanismo eliminador, determinada esta última por la historia previa del pulmón con respecto a infecciones y exposición a la sustancia irritante específica.

Further Observations of Lung Changes Associated with the Manufacture of Alumina Abrasives[1]

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AN INITIAL REPORT on the clinical, radiological, and pathological aspects of the lung changes encountered in certain men employed in the manufacture of alumina abrasives has already been published (1). A further report on the chemical aspect of the disease has been read but as yet is unpublished (2). Twelve months have elapsed since the first report was read and during this interval we have had a further period to study in greater detail the symptomatology and clinical features of the disease, as well as serial radiographs.

Our initial report presented two groups of cases, well established and early. In the former group there were 23 cases, whereas there are now 34. In the early group there were 12; there are now 38. The classification of well established disease is based on clinical and radiological evidence. All patients with symptoms have changes of moderate to extreme degree demonstrable by x-rays. Others may have few symptoms but the x-ray picture shows a widened mediastinum or marked diaphragmatic adhesions associated with considerable parenchymal shadowing. Our experience has demonstrated that such persons usually progress to a more serious type of disease. In the early cases, on the other hand, symptoms are not present nor do the x-ray films show marked distortion of the diaphragm or mediastinal widening.

Occupational History: In reviewing the occupational histories of the well established cases, it is to be noted that the greatest number of employees working in the arc furnace rooms are directly associated with the furnaces as furnace feeders, and it naturally would be expected that from this group one would get the greatest number of cases. We have found, however, that there is a definite hazard encountered by those men who change the furnace pots and also by instructors, who are exposed to sufficient fumes to acquire the disease in certain instances. It has been pointed out in our previous paper that bin men and crane men are also subject to a definite hazard. The summary of exposure for 30 well established cases in men who have been directly associated with the feeding of furnaces and who frequently interchange jobs with hot change men is as follows:

Less than 2 years	2 cases
2 years and less than 3	5 cases
3 years and less than 4	8 cases
4 years and less than 5	4 cases
5 years and less than 6	0 cases
6 years and less than 7	2 cases
7 years and less than 8	4 cases
8 years and less than 9	1 case
9 years and less than 19	4 cases

Four men gave no history of exposure as furnace feeders. One was a crane operator for five years, and had no other exposure. Another was a hot change man for four years but never had experience feeding the furnaces; in addition, he was a crane operator for six months. A third worked as a hot change man for five years before development of the disease. The fourth patient was a bin man working above the furnaces for three years and two months, in whom serious disease developed.

The longest period of exposure was nineteen years, four as a furnace feeder and fifteen as an instructor in the department; the shortest was eighteen months, seven as

[1] Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

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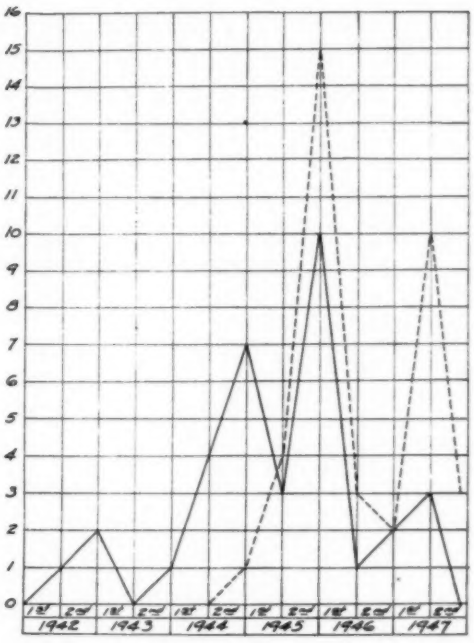
furnace feeder and eleven as a hot change man. There are several men in the various plants who have worked as long as nineteen years continuously as furnace feeders and who have shown no distinctive x-ray changes to suggest that they are suffering from this disease.

Relationship of Disease to War Period: Since the disease was discovered during the war years, it was surmised that there would be a rapid fall in its incidence following the cessation of hostilities, because of reduced exposure since, in the first place, the men would be working with furnaces which were not fusing pigs as rapidly, and secondly they would be working in an atmosphere where fewer furnaces were operating. It is to be noted, however, that 3 cases were discovered in 1942, and 1 case was discovered in 1943. Following this, we began to survey the plants, and in 1944 a total of 11 cases were discovered. There was a drop during the first part of 1945. The survey then continued during the year, with discovery of 13 cases. The survey work was again reduced and in 1946 only 3 cases were detected. Two well established cases were discovered in 1947, and 3 cases advanced from the early to the well established class. Early cases were not seen until the survey had been well organized. No cases that we considered to be in the early group were discovered prior to 1944 and only 1 case which could be classified as early was found in the latter part of that year. With the survey started, in 1945 a total of 18 cases were found in the early group, and in 1946 5 cases were discovered. There is seemingly some discrepancy between these figures and the initial report, inasmuch as a total of 24 cases to December 1946 are being shown, whereas previously there were only 12. This is due to the fact that with increased knowledge of the disease, and a review of previous films, an additional 12 cases have been classified as early, these not having been reported previously. With the institution of regular examinations at intervals of six months, we again find a large increase in 1947, and to



Graph 1. Cases diagnosed in six-month periods, 1942 to 1947. The solid line indicates well established cases (34); the broken line early cases (38).

Nov. 1 of that year a total of 13 early cases have been diagnosed. On checking our records previous to 1942, we find 2 men with experience as furnace feeders showing definite x-ray change diagnostic of disease. One of the men had fifteen years' experience prior to 1936 with no exposure since that time; the other was removed from exposure in 1940. Although we do not have a large series of cases, there is sufficient evidence to show that the disease was present previous to the war years and was not recognized.

The accompanying graph shows the well established and early cases which were diagnosed in six-month periods between 1942 and 1947.

Progression of Disease after Removal from Furnaces (34 Well Established Cases): Seven patients were in desperate condition when first seen and all of them died within a relatively short period of time. Three cases have been too recently diagnosed to assess any extension at present. The following table classifies the remaining 24

Years Removed from Fume Exposure	No. Cases	No Change	1 Plus	2 Plus	3 Plus	4 Plus
1 and less than 2	5	1	4			
2 and less than 3	14		3	5	4	2
3 and less than 4	0					
4 and less than 5	1					1
5 and less than 6	1		1			
6 and less than 7	1		1			
7 and less than 8	1	1				
11 and less than 12	1		1			

cases with extension of disease designated 1, 2, 3, and 4 plus. All of these men have been removed from furnace fume exposure for at least one year.

We have also classified the roentgenograms according to changes in the mediastinal width, development of adhesions, and emphysematous blebs, again excluding the 7 desperate cases. There are 4 cases of the remaining 27 showing development of diaphragmatic adhesions without increase in mediastinal width during the time they have been under observation; 15 cases showed development of adhesions, or very definite increase in adhesions, with some increase in the width of the mediastinum. In 2 instances, there was widening of the mediastinum with no definite change in the diaphragmatic shadows. The other 6 cases showed no change in mediastinal or diaphragmatic shadows during the observation period. The maximum increase in the width of the mediastinum has been 3.5 cm. at the level of the 2nd anterior rib. In this particular case the change occurred in a period of two years and five months. All films were taken at 6-foot distance. Ten cases showed very definite roentgen evidence of emphysematous blebs.

Employees Removed from Exposure with Negative Films: We have been interested to learn whether or not the disease would develop after an employee has been removed from exposure to fumes. The following history illustrates such an instance.

This person began work at Plant A in June 1941. His occupation was that of general laborer in the arc furnace department. In August 1941, he became a furnace feeder in the same department and continued at this job for six months. In February 1942, he became an instructor in the arc furnace department and continued there until July 1944, when he enlisted. He remained in the army until June 1946. At that time he returned to Plant A and worked as a furnace feeder for approximately five months. In October 1946, he was removed to the yard as a general laborer and in May 1947 he left the plant because of lung changes noted.

On relating his history this man has no complaints. Enquiry, however, reveals that he is somewhat short of breath, though he states that he has improved somewhat in this respect since he left the furnace job. His weight, which was 157 lb. in the army, is now 132 lb. He believes this loss of weight is entirely due to the heavy work in which he is engaged at the present time. Physical examination of the chest is negative. X-ray reports are as follows: Enlistment film, dated April 24, 1944, was reported negative, and a review of this film shows no change suggesting the present disease. A second film dated Nov. 12, 1945, while the man was still in the army, shows a normal heart and diaphragm. Hilum shadows appear unchanged when compared with the enlistment film. Above the 3d rib on either side there is a change not noted in the enlistment picture, showing a slight tendency toward granulation. The apical markings suggest a limited degree of emphysema. Stereoscopic films, dated February 1946, show no change in the heart, diaphragm, or mediastinum, when compared with the previous film. Both lungs show granular shadowing above the 3d rib. These films do not show the apices as clearly and the emphysematous change is not as clear. The next film, taken July 9, 1946, after resumption of employment at Plant A, shows the heart and diaphragm to be the same as previously. Hilum shadows are not extensive. There is a definite granular change above the 3d rib on either side, with further changes in the right apex especially, suggesting emphysematous blebs. The granular shadowing is more pronounced than in the February 1946 film taken shortly before discharge from the army. Another film, taken on Oct. 6, 1947, shows the heart shadow to be unchanged. The left diaphragm shows a tent-like adhesion at the dome. Both lungs show granular shadowing above the 4th ribs, with the heaviest markings noted in the 1st interspaces. There is change in both apices suggesting emphysematous blebs. Compared with the film taken in July 1946, the granular shadowing is materially increased. Compared with the film of April 1944, the whole process appears new. The condition has gradually increased since November 1945, at which time the disease was first noted roentgenographically.

This man enlisted in April 1944, after

the exposure noted above. He showed no evidence of disease until November 1945, and although he has had only a short period of exposure since, he has shown a gradual progression of disease to the present time.

Symptomatology: In view of the fact that the early cases are singularly free of symptoms, only the well established group of 34 cases is being considered here. A great number of employees doing this particular type of work complain of a very mild morning cough with a small amount of dark colored sputum. In the group of 34 patients, 21 complained of cough. In the majority of these, the cough was not severe. In one case it was considered to be moderate; in only one was it extremely severe. In that case it was sufficiently bad to warrant a bronchoscopic examination, the result of which was negative. Twenty-one patients complained of sputum but in only 4 was it excessive.

There were 7 patients who complained of pleuritic pain and, in view of the number of pneumothoraces noted, this seemed rather peculiar. However, it frequently occurred that a patient would show a pneumothorax on x-ray examination, and on subsequent follow-up it would be found that he had experienced no pain at the time of its development.

Eleven patients of the 34 complained of substernal pain. This complaint was encountered only in far-advanced disease. In some cases it was extreme; in others, moderate.

There were 23 patients of the group who complained of shortness of breath. In 5 cases, this was minimal; in 2, moderate; in 3, quite severe; in 13, it was extreme. With bilateral pneumothorax, shortness of breath was always extreme, the patient complaining of a sudden increase in this symptom, which had been present for some time. This finding has been correlated with vital capacity. In the 7 patients who were in extreme condition when first seen, vital capacity tests were not done. In the remaining cases, vital capacity ranged as follows: 2 cases between 30 and 40 per cent; 2 cases between 40 and 50 per cent; 8 cases between 50 and 60 per cent; 3 cases between 60 and 70 per cent; 4 cases between 70 and 80 per cent; 3 cases between 80 and 90 per cent, and 5 cases between 90 and 100 per cent.

Physical Examination of the Chest: Of the 34 well established cases, 7 showed impairment of resonance to a greater or lesser degree. In 12 patients, râles were elicited, but in 7 of these they were heard only intermittently. Rhonchi were noted intermittently in 5 cases. Pleural friction rubs were present in 4 patients. Pneumothorax was observed in 13 cases; in 9 instances, this was bilateral, that is, both lungs showed partial collapse at the same time. In 2 other instances, both lungs were involved, but alternately, while in 2 cases the pneumothorax was unilateral. It is interesting to note that 7 of the 9 patients with bilateral pneumothorax died. The 2 remaining are totally incapacitated and on compensation. Of the 2 who had alternating pneumothorax, 1 died; the other had complete re-expansion of his lungs and is now working. Of the patients with unilateral pneumothorax, 1 is incapacitated; the other is working.

Among the 7 patients who died, the average loss of weight up to the time of their last examination was 13.5 lb. The average loss of weight in the group of 8 men who are totally incapacitated and on compensation was 8 lb. The maximum loss was 24 lb., the maximum gain was 15 lb. after the patient was placed on compensation. Of the remaining group of 19 patients, 8 have gained weight, 5 have lost, and 6 have shown no change.

Acute Infections Associated with the Disease: We have reviewed all the records of the well established and early cases and we find one case with a history of pneumonia in February 1945. He was diagnosed as having early disease in June 1946. A second patient had atypical pneumonia during July and August 1945, and a diagnosis of early disease was made in September 1945. In another instance a patient had severe bronchitis in December 1943, and a diagno-

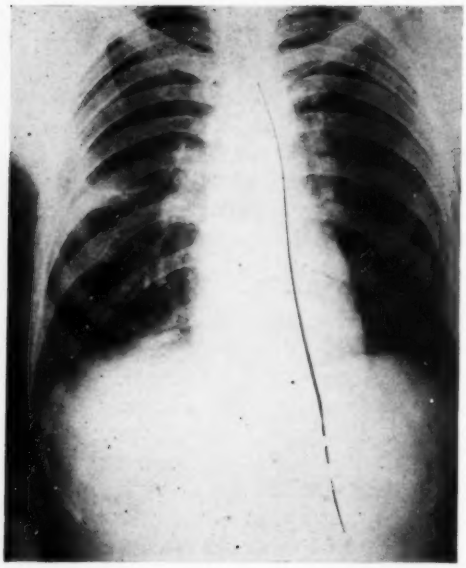


Fig. 1. Case I. Feb. 26, 1942. Right intrapleural pneumothorax, as well as interlobar pneumothorax within partially collapsed right lung.

sis of well established disease was made in January 1944. In the very first case which we saw, in February 1942, there was an acute infection, but not serious enough to make the patient go to bed. This condition resolved in normal fashion and it is doubtful if it had any influence on the occupational disease. In another case, diagnosed in August 1945, a right lower lobe pneumonia developed in December 1945. A chest film obtained subsequent to this attack showed shadowing, presumed to be fibrosis, in the right base, and this has continued, along with marked displacement of the mediastinum to the right as well as marked elevation of the right diaphragm. It is possible that the infection may have had some influence on the progress of the disease. There is, however, little evidence to prove that acute infection plays any major part in the progression of this disease as we have seen it.

Fume Exposure: The fume particles to which this group has been exposed, as demonstrated by the electronic microscope, have been studied by Jephcott, Johnston, and Finlay. They range from a few hundredths to nearly half a micron in diameter. Analysis by x-ray diffraction shows that the fume consists mainly of amorphous material.

A chemical analysis of Arkansas bauxite indicates that it contains Al_2O_3 80 per cent, SiO_2 5 per cent, and a further group of chemicals in rather small amounts. The fume, on the other hand, shows Al_2O_3 50 per cent and a relative increase in SiO_2 to 35 per cent. An analysis of the lung ash from postmortem material shows the same relative proportion of alumina and silica as the fume.

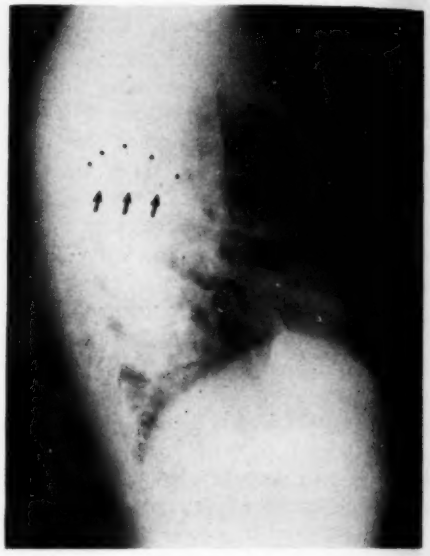


Fig. 2. Case I. March 5, 1942. Lateral film showing interlobar pneumothorax with fluid level.

CASE HISTORIES

CASE I: This was the first case seen, in February 1942. B. K., age 33, had spent eight years as a furnace feeder. He reported for examination because of a sudden pain in the right chest when he was trying to remove a car from a snowbank. He stated that he had had a rather severe chest cold previously, and at the time of examination he had considerable cough and sputum. X-ray showed a pneumothorax on the right side. Below this, in the 3d interspace, was an indefinite ringed shadow (Fig. 1). The following month a lateral film (Fig. 2) showed the shadow to lie posteriorly in the chest and to contain a fluid level. It was thought to represent an inter-

lobar pneumothorax with fluid. Further x-ray examination on March 23, 1942, showed the pneumothorax to have disappeared, but the interlobar shadow was still present, showing a fluid level.

When first seen, this patient was advised to give up his job as a furnace feeder. After recovery from his initial illness, he returned to work in the laboratory of the same plant. He was re-examined on Nov. 27, 1942, at which time he complained of cough and sputum. X-ray examination, in addition to granular shadowing in the upper portion of both lungs, showed a rounded shadow in the 2d interspace on the left side containing a fluid level. This was thought to be an interlobar pneumothorax on the left. Recovery from this illness was uneventful and the patient returned to his work in the laboratory, where he has remained to the present time. His lung shadowing increased slightly to 1945 (Fig. 3). However, he is now free of symptoms except for shortness of breath noted on extreme exertion. His vital capacity is 86 per cent of normal. Over the past two years there has been no extension of the disease.

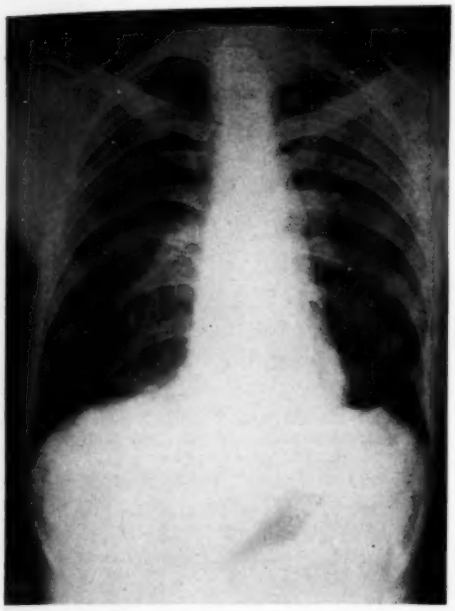


Fig. 3. Case I. Nov. 3, 1945. Disease apparently stabilized.

CASE II (Fig. 4): J. D., age 25, was an Al_2O_3 furnace feeder five years and two months, prior to November 1941. He was first seen on Aug. 8, 1942, giving a history of increasing dyspnea since December 1941. He died May 25, 1943.

CASE III (Fig. 5): P. H., age 32, was an Al_2O_3 furnace feeder for two years and eight months. He was first seen on Aug. 25, 1942, complaining of

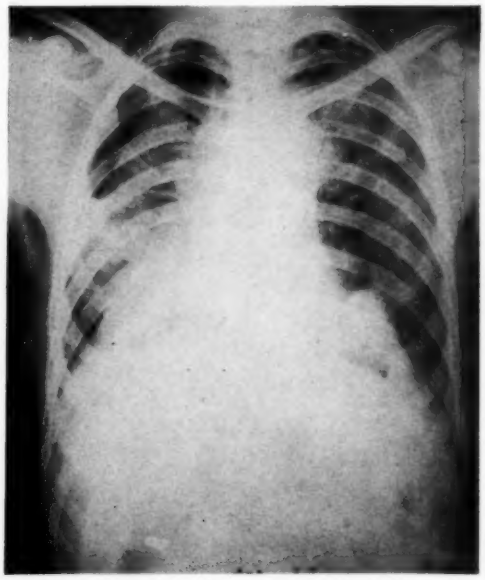


Fig. 4. Case II. Nov. 26, 1942. Bilateral pneumothorax. The heart and mediastinal shadows are wide, there is marked distortion of the diaphragm, and lace-like shadowing is present throughout both lungs.

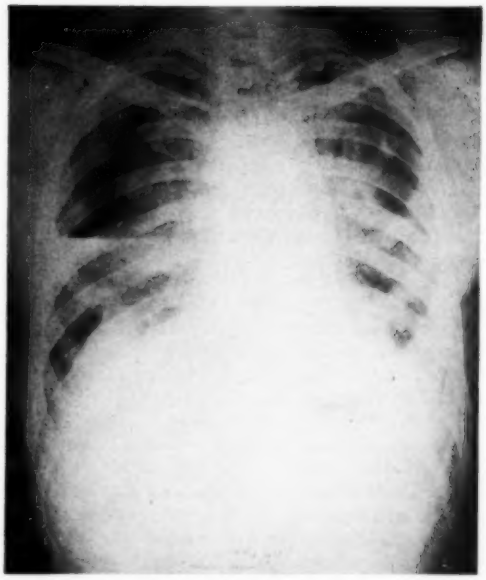


Fig. 5. Case III. March 25, 1943. Bilateral pneumothorax with small effusion on right side, diaphragmatic adhesions, and parenchymal shadowing. The mediastinal shadow widened as the lungs tended to re-expand.

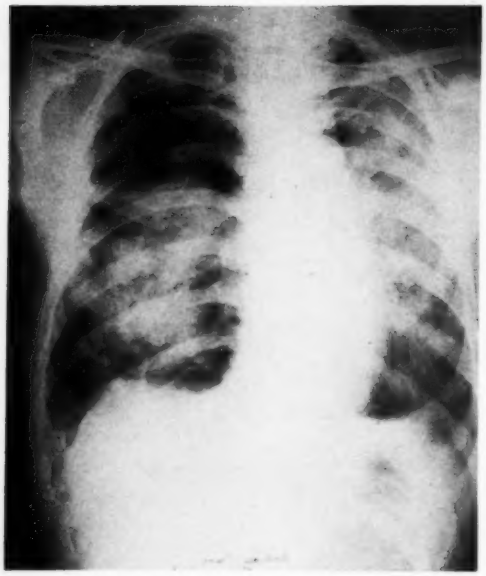


Fig. 6. Case IV. May 8, 1944. Bilateral pneumothorax, adhesion of left diaphragm, and marked granular shadowing involving both lungs.

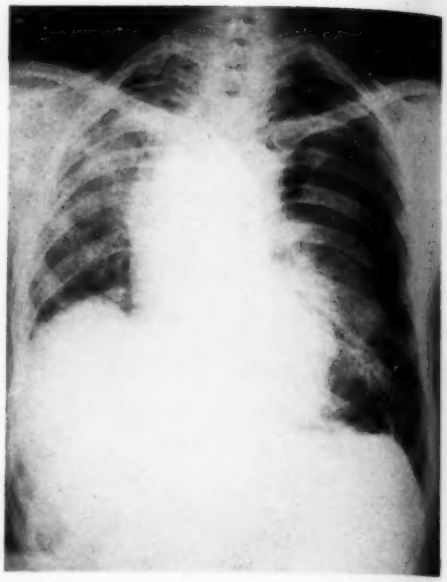


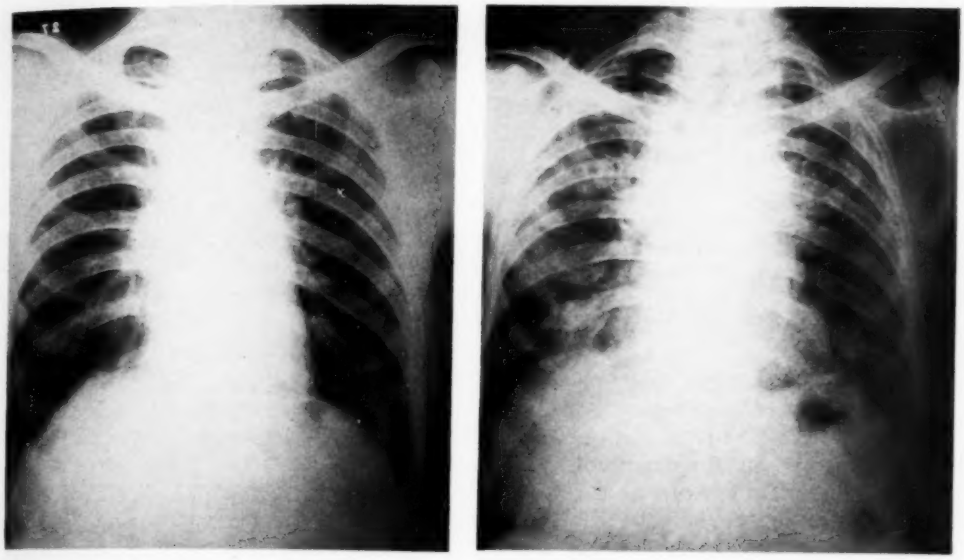
Fig. 7. Case V. Aug. 24, 1944. Bilateral pneumothorax, elevation of right diaphragm, and parenchymal changes similar to those in previous cases.

shortness of breath for the past nine months and pain in the left chest for two weeks. He died Nov. 23, 1943.

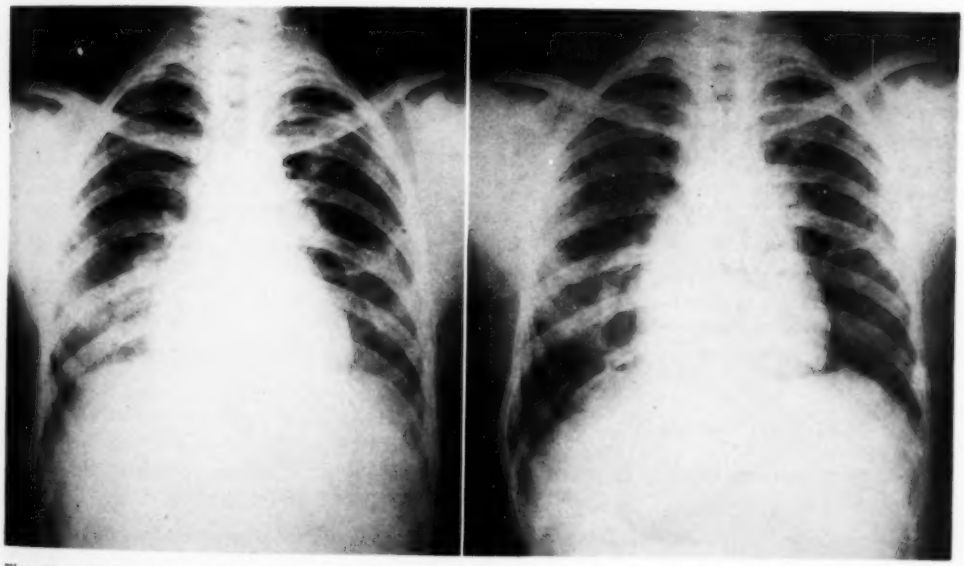
CASE IV (Fig. 6): W. P., age 41, was an Al_2O_3 furnace feeder two years and five months. He was first seen on May 8, 1944, having been ill since December 1943, with pain in the lower chest, weakness, and dyspnea, which suddenly became worse on May 4. He died May 10, 1944.

CASE V (Fig. 7): J. F., age 42, was an Al_2O_3 furnace feeder for three years. He was first seen on May 15, 1944, with a history of feeling poorly for the past six months. His chief complaints were weakness, increasing shortness of breath, and substernal discomfort. He died July 14, 1945.

CASE VI (Fig. 8 and 9): N. C., age 40, was first seen on Aug. 24, 1944. His occupational history showed that he had been a furnace feeder for eight and a half years and then a crane operator for two and a half years. A film at this time showed a hump of the right diaphragm. The heart appeared normal in size, but the mediastinum was widened. Granular shadowing was noted above the 3d rib on either side. There were no symptoms and physical examination was negative. In June 1945 symptoms were still absent and physical examination was again negative, but comparison of a film made at this time with the earlier one showed further widening of the mediastinum, with some increase in the granular shadowing over the upper third of each lung. The patient was now removed from the vicinity of the furnaces to an outside job. He was re-examined in September 1945, at which time he complained of cough with sputum. No history of pain could be elicited, and physical examination was negative. X-ray examination, in addition to the changes noted in the previous film, showed a small pneumothorax confined to the upper and outer portion of the right lung. The pleural surface of the collapsed lung appeared quite irregular. The patient returned in October 1945, stating that during the interval he had had a chest cold. He did not complain of shortness of breath. Physical examination of his chest was negative. A film showed that the right lung had completely re-expanded, but a pneumothorax of the left lung was demonstrable, confined to the upper and outer portion. The granular shadowing now extended as low as the 4th rib on the right and to the 3d rib on the left. Re-examination in December 1945, showed the left pneumothorax to be persisting. At this time shortness of breath was a marked symptom and the man was forced to discontinue work. In February 1946, he complained of increasing cough, sputum, and shortness of breath. X-ray examination at this time showed the left lung to have completely re-expanded. There was tremendous increase in mediastinal width and a generalized shadowing throughout both lungs, more extensive on the right than the left. The condition gradually deteriorated and when the patient was seen again, in March 1947, he complained of extreme shortness of breath. However, his weight remained constant. Extreme mediastinal widening was demonstrable and there was distortion of the



Figs. 8 and 9. Case VI. Fig. 8 (left). Oct. 24, 1944. Routine film. Patient was free of symptoms. Fig. 9 (right). March 12, 1947. Marked progression of disease, with changes in heart, diaphragm, and mediastinal shadows, as well as emphysema involving bases and right apex.



Figs. 10 and 11. Films taken at 6 feet on expiration (Fig. 10) and inspiration (Fig. 11) to demonstrate paradoxical movement of mediastinum.

diaphragm. Marked granular changes were present throughout both lungs, with evidence of emphysema in the upper portion of the right and in the bases. Progress was unfavorable from this date, and in July 1947 a right pneumothorax developed, with marked displacement of the mediastinum. After some time in the hospital, the lung practically re-expanded, but death due to a failing heart ensued on Aug. 19, 1947.

CASE VII (Figs. 10 and 11): A. M., age 25, has an interesting history from the standpoint of pneumothorax. He was first seen on Nov. 22, 1944, with a

history of six and a half years' experience as a furnace feeder. On his initial examination he had a left pneumothorax, which continued to January 1945, when it re-expanded. A left pneumothorax again developed in September 1945 but re-expanded the following month. The patient was observed at monthly intervals, and in March 1946 he was again found to have a pneumothorax on the left, which continued until April 1947. In the meantime, x-ray examination in June 1946 showed a right pneumothorax, which quickly re-expanded. The left pneumothorax, persistent since March 1946, was found to have disappeared in May 1947. It recurred in June 1947 and has persisted to date. The patient is totally incapacitated.

An interesting feature of some of these cases is observed under the fluoroscope. Normally one notes that the mediastinal shadow narrows on inspiration and widens on expiration. However, with this disease, when fibrosis of the lung is marked, the mediastinal shadow tends to narrow on expiration (Fig. 10) and widen on inspiration (Fig. 11).

SUMMARY

A review of the case histories of men who have been employed in the manufacture of alumina abrasives shows that there are at the present time 34 well established and 38 early cases of lung involvement associated with this industry. Furthermore, the review indicates that the disease was present previous to the war but had not been recognized. In one case, a man leaving employment of the plant with a negative chest film showed evidence of disease one year later. It might therefore be concluded that some of the cases of early disease discovered since the war may have developed from exposure during the war years, when fume concentration was especially heavy. It would follow that in certain individuals who have a susceptibility, the disease may develop, under given conditions, in the future.

Evidence suggests that once the disease becomes well established progression is often rapid, and complete disability may shortly result. By frequent examination and removal of men from exposure on discovery of the earliest x-ray change, though some may show progression of disease, the chance is that the condition will become stabilized at a certain point before disability is serious.

On reviewing the symptomatology and physical examination, it is noted that symptoms and abnormal findings are present only in the well established group. X-ray examination, with high-grade and usually stereoscopic films, is necessary to make a diagnosis in the early cases. Furthermore, it is to be noted that acute infections associated with the disease appear to play no major part in its progression.

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SUMARIO

Nuevas Observaciones de las Alteraciones Pulmonares Asociadas con la Fabricación de los Pulidores de Aluminio

El repaso de las historias clínicas de los obreros empleados en la fabricación de pulidores de aluminio revela que actualmente hay 34 casos bien establecidos y 38 incipientes de patología pulmonar asociada con dicha ocupación. Además, el estudio indica que la enfermedad ya estaba presente antes de la guerra, pero no había sido reconocida. Por ejemplo, un individuo que salió del establicimiento con una radiografía torácica negativa reveló signos de la enfermedad un año después. Cabría, por lo tanto, deducir que algunos de los casos incipientes descubiertos después de la guerra pueden haber tenido su origen en la exposición de los años de guerra, cuando la concentración de vapores fué por demás intensa. De esto se colegiría que en ciertos

individuos susceptibles, la enfermedad puede presentarse, en ciertas circunstancias dadas, en el futuro.

Los datos disponibles sugieren que, una vez establecida la dolencia, la agravación es a menudo rápida y puede ir seguida de incapacidad total en breve plazo. Con exámenes frecuentes y separación de los obreros de la exposición a la sustancia al descubrirse los primeros signos radiográficos, lo más probable es que el estado se estabilice en cierto punto antes de que la incapacidad sea grave.

Al repasar la semiología y datos del examen físico, obsérvase que sólo hay síntomas y hallazgos anormales en el grupo bien establecido. Los sintomas comprenden tos, expectoración, dolor pleurítico o subesternal y disnea. Los signos radiográficos son ensanchamiento del mediastino, aparición de adherencias diafragmáticas y vesículas enfisematosas. En 13 de los 34 casos bien establecidos se presentó neumotórax. Para el diagnóstico en los casos tempranos resulta necessario el examen con los rayos X, con películas de alta calidad y por lo general estereoscópicas. Además obsérvese que las infecciones agudas asociadas con la enfermedad no desempeñan aparentemente mayor papel en su agravación.

Delayed Chemical Pneumonitis or Diffuse Granulomatosis of the Lung Due to Beryllium[1]

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A MORE SUITABLE title for this presentation would have been, "Pulmonary Changes Occurring Among Beryllium Workers." Sufficient evidence seems to have accumulated for us to consider beryllium or its compounds to be etiological factors; still, absolute proof of this assumption is not yet available. It was necessary, first of all, to prove that beryllium is toxic in the amounts and compounds to which the individuals were exposed. Next, the opportunity for exposure had to be established, and all other causative factors ruled out. Third, the cases had to show a similarity of clinical findings, roentgen pattern, and pathological changes postmortem. Fourth, the suspected toxic agent had to be shown to be present in the tissue. Fifth, the disease must be produced experimentally in animals, if possible. These conditions have all been fulfilled, with the possible exceptions of ruling out other causative agents and producing identical lesions in the lungs of animals exposed to this element. Experimentation has, however, now reached a point where it may be possible to meet these requirements as well.

Opportunity for exposure to beryllium starts in the beryl mines. In plants engaged in extracting beryllium from the ore and in the production of beryllium salts and oxides there has been definite evidence of disease among employees. The same has been true in metallurgical plants where beryllium has been used as a constituent in the production of alloys. Cases have been reported where the phosphors that are used in coating fluorescent lamps and neon tubes were being processed. Others have been discovered where the lamps were manufactured and where neon tubing was being bent. At least one case has arisen in the radio tube industry, and a few where the metal or its oxide was being ground. Beryllium or its compounds may be found in chemical and pharmaceutical plants. It is a possible hazard in research laboratories. Its use has been reported where gas mantles and some ceramics are made. There are undoubtedly many other instances which have not been uncovered. It must be noted that not all of these industries have experienced the development of pulmonary disease among their workers. In those that have, the symptomatology, x-ray pattern, and pathology have been so similar that a common denominator is suspected, this denominator being beryllium or one of its compounds.

In reviewing the literature regarding the toxicity of this substance, one is quite surprised to find a number of articles dealing with the subject. Most of these appear in European journals between 1933 and 1942. Very little beryllium was being used in America prior to the recent war. It was not brought to the attention of the medical profession until 1943. In that year, under the title, "Chemical Pneumonia in Workers Extracting Beryllium Oxide," Van Ordstrand, Hughes, and Carmody reported three cases in the Cleveland Clinic Quarterly (1). Kress and Crispell, writing in the Guthrie Clinic Bulletin in 1944 (2), described a similar chemical pneumonitis occurring among employees working in fluorescent powders containing beryllium. In 1945, Van Ordstrand and his associates published a second paper, reporting a much larger group of cases, in the J. A. M. A. (3).

[1] Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947

[2] Roentgenologist, Salem Hospital, Salem, Mass.

A few other articles on the subject, as well as these mentioned, dealt with what is now accepted as the acute type of response.

During this same period, several cases of a peculiar chronic pneumonitis were being studied among workers employed in the fluorescent lamp industry. Hardy and Tabershaw compiled the clinical manifestations from 17 of these cases and reported them in the Journal of Industrial Hygiene and Toxicology (4), using the title, "Delayed Chemical Pneumonitis Occurring Among Beryllium Workers." Higgins (5), in his report of these same cases, referred to them as "Sarcoidosis." After intensive study, including animal research as well as clinical, Leroy Gardner (6) in his notes offered the title, "Generalized Pulmonary Granulomatosis." A most complete presentation and discussion of both forms of the disease were given at the Saranac Symposium in September 1947. At this meeting, it was deemed advisable to agree upon some standard nomenclature. Accordingly, the acute type was designated, "Acute Pneumonitis of Beryllium Workers," and the chronic form, "Pulmonary Granulomatosis of Beryllium Workers" (7).

An excellent study of cases may be obtained from the references mentioned. A brief review of the findings, however, is necessary before presenting the roentgenological aspects with which this paper is principally concerned.

ACUTE PNEUMONITIS

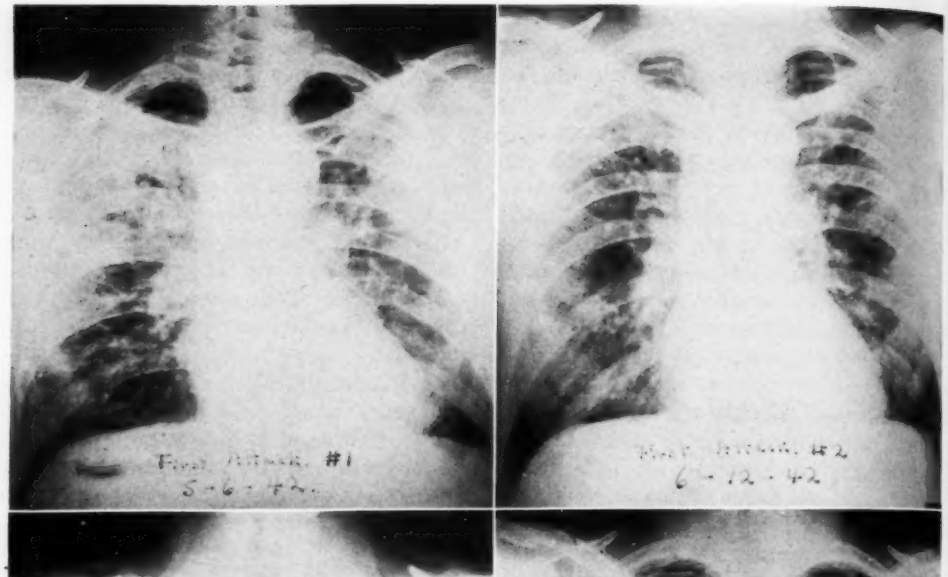
In recording the findings in 38 cases, of which 5 terminated fatally, Van Ordstrand and his associates brought out the following facts: The incidence and severity were proportionate to degree of exposure and chemical irritation of dusts and fumes. No single work station could be isolated, and the duration of exposure varied considerably. Most of the patients recovered within a few weeks or months following rest and removal from exposure, but recurrence took place with re-exposure. The onset was insidious but was not a delayed reaction. It was characterized by cough, and occasional dull, burning substernal pain. Dyspnea soon followed the onset of cough. Cyanosis became evident in some cases. A few patients complained of abnormal taste. Anorexia with loss of some weight was a consistent finding, usually accompanied by increasing fatigue.

The significant physical findings were the absence of signs of infection, a rapid pulse, and very little elevation of temperature. No pathogens were found in the sputum.

Pathologically, the findings were those of atypical pneumonitis, pulmonary edema, and hemorrhagic extravasation. Plasma cells were found in large numbers, but there was a relative absence of polymorphonuclear infiltration.

PULMONARY GRANULOMATOSIS

Hardy and Tabershaw, after describing the histories of 17 cases, which they designated as "delayed pneumonitis," tabulated the clinical findings. Nearly all of the symptoms listed under "Acute Pneumonitis" appear in this table and represent the highest percentage of symptoms recorded in the "pulmonary granulomatosis" group. The time factor and relation to onset are, however, distinctly different. When adequate exposure data have been obtained, the same correlation between concentration or magnitude of exposure and disease will be found to exist in the chronic reaction as in the acute. No single work station can be isolated, but certain types of operations have certainly proved to be more productive of cases. The most pronounced variation, however, is the delay in onset, which may be as long as six years after opportunity for exposure has ceased. The duration is measured in months and years rather than weeks and months, and recovery does not follow removal from exposure. Loss of weight is a prominent and rather constant finding even early in the disease, though signs of respiratory distress are equally significant. Cyanosis, low blood pressure, and clubbing of the fingers are frequent physical findings,



Figs. 1–4. Acute pneumonitis following exposure to beryllium oxide. See also Fig. 5.
Fig. 1 (upper left). Roentgenogram during first attack; areas of consolidation simulating bronchial pneumonia. Fig. 2 (upper right). Roentgenogram after five weeks' interval, showing granular density after clearing of consolidated areas. Fig. 3 (lower left). Same case after recovery from attack, with essentially normal findings. Fig. 4 (lower right). Roentgenogram following second exposure to same substance.

as well as those mentioned under "Acute Pneumonitis."

There are now more than 50 recognized cases of pulmonary granulomatosis in this series, with reports on several necropsies. The lesions seen in the so-called chronic pulmonary granulomatosis occurring in beryllium workers are recognized grossly as very small pinhead-sized, whitish nodules found diffusely throughout the lobes of the lung. The draining lymph nodes occasionally are enlarged and may show areas of a granular, grayish white necrosis, partially or completely replacing the lymph node. Microscopically, the lesions are found both within the air sacs and in the supporting framework of the lung, and it is thought that several different stages of development

are to be recognized. The earliest lesion is usually seen within the alveoli and consists of aggregations of large mononuclear cells, so-called histiocytes, associated with a moderate amount of edema. Later, nodules within the framework of similar histiocytes are seen, which are surrounded by a zone of lymphocytes and occasional plasma cells. The next phase is that of necrosis within the central masses of the histiocytes occasionally associated with the presence of foreign-body-type giant cells and with increasing fibrosis about the periphery of the granuloma, accompanied by a moderate accumulation of lymphocytes and plasma cells. The end stage is represented by an area of marked hyalinization. With special stains the reticular framework within the early granulomas is seen to be destroyed in the stages in which necrosis is present, and in some of the earlier granulomas there appears to be a distinct increase of reticulum, either arising from blood vessels or possibly being formed by histiocytes.

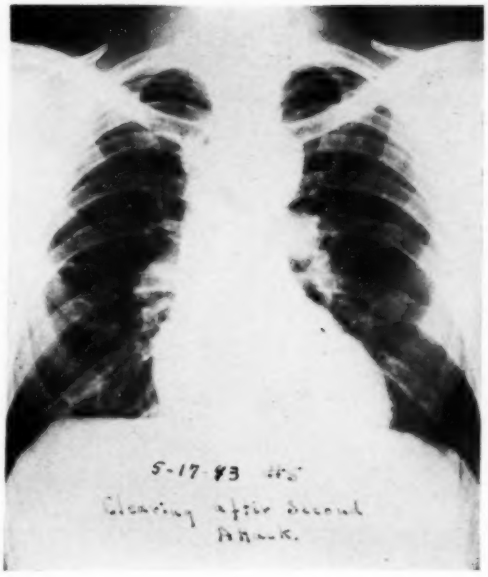


Fig. 5. Same case as Figs. 1–4. Roentgenogram following recovery from second attack. Note residual fibrosis.

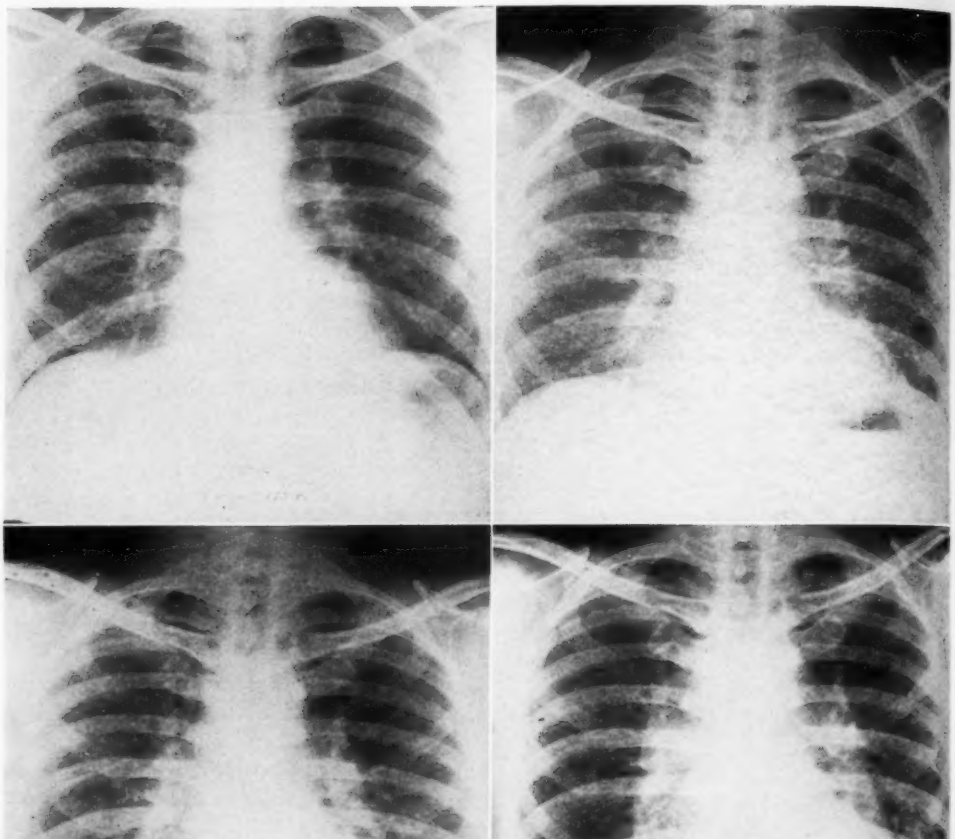
SUBACUTE OR ATYPICAL PNEUMONITIS WITH GRANULOMA FORMATION

Though only two forms of the disease have been recognized, it may be necessary to accept a third based on the type of exposure and presenting roentgenograms. In 3 cases with exposure to the dust from a compound containing beryllium oxide, pulmonary changes have developed which resemble somewhat the acute type but have a delayed onset and a more progressive course, similar to the chronic form. There is, however, no proof at present that in individuals suffering from the acute form, the chronic may not sometimes develop. If so, these cases may represent such a transition.

ROENTGEN PATTERN

The roentgen findings are naturally dependent upon the pathological changes taking place. Those described by Van Ordstrand and his associates as occurring in "acute pneumonitis" have characterized the few cases seen in this series. A diffuse haziness or ground-glass density similar to that of pulmonary edema made its appearance in both lungs one to three weeks after onset of symptoms. This stage was followed by areas of soft infiltration similar to those seen in bronchial pneumonia and accompanied by prominent linear markings and hilar enlargement. These areas appeared to absorb, and small nodules made their appearance in both lungs. These cleared almost completely after one to four months, and usually before complete subsidence of symptoms. One or two of our cases showed some residual linear fibrosis. There is no mention of this in the report of Van Ordstrand *et al.*

In this presentation, we are principally concerned with the chronic form, since nearly all the cases we wish to report fall into this group. It has been our privilege to follow most of them roentgenologically and clinically with the family physician. The earliest cases were seen in 1942 and 1943 and were variously diagnosed as sarcoidosis, pneumonitis of unknown origin, and sarcoid-like pneumonitis by the author, other radiologists, and chest phy-



Figs. 6–9. Chronic pulmonary granulomatosis.
Fig. 6 (upper left). Earliest recognizable stage; granularity fine and indistinct. Roentgenogram made at least two years after exposure to fluorescent powders. Fig. 7 (upper right). Eighteen months later. Granularity more distinct. Fig. 8 (lower left). After nearly two years. Granularity with some nodularity and suggestion of reticulation. Fig. 9 (lower right). Three years after onset. Distinct nodularity, though fine.

sicians. During the year 1943, however, an occupational hazard was suspected which led to the investigation and report by Hardy and Tabershaw. In this report, Sosman and Wilson offered what is thought to be the earliest published description of the roentgen findings based on the chest roentgenograms of 12 of the original 17 cases. They may be quoted here:

"Reviewing the x-rays of 12 of the 17 patients, the roentgenological appearances fall into three distinct stages, not counting the variable latent period (3 months to 3 years) in which the lungs appear normal.

"*Stage 1.* The earliest recognizable variation from the normal is a fine diffuse granularity, presenting a fine sandpaper appearance, which under the magnification of a reading glass suggests a sand storm. There are no increased linear markings, no nodules, no coalescent lesions, no pleural thickening, and no

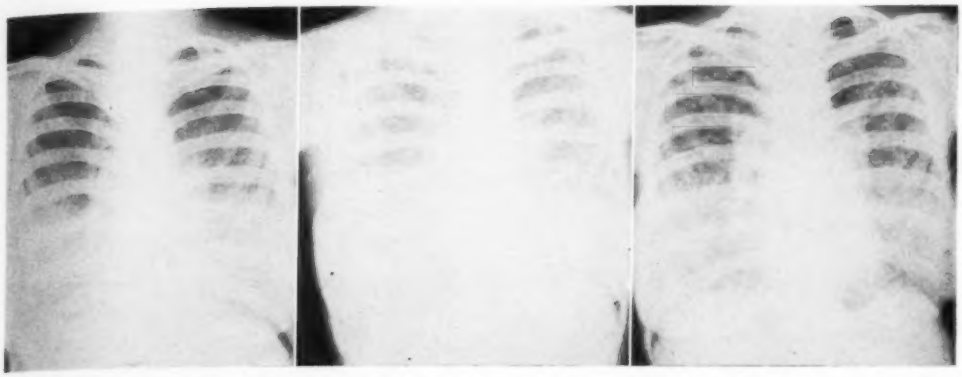


Fig. 10–12. Pulmonary granulomatosis following exposure to fluorescent powders. Onset of symptoms four years after exposure. Fig. 10 (left). Early roentgenogram showing fine granularity with some nodularity. Fig. 11 (center). One year later. Nodularity more distinct. Fig. 12 (right). Eighteen months after onset. Nodularity more pronounced, with increased size of nodules and areas of intervening emphysema. Nodularity at the hila.

pleural effusions. The appearance is not the smooth homogeneous ground-glass appearance of pulmonary edema or consolidation, but distinctly particulate in appearance. It is uniform and diffuse, extending to the periphery and includes the apices, although at first glance the apices seem to be spared. The hilar vascular shadows are usually normal and distinct in this stage.

"*Stage 2.* The second stage is characterized by a diffuse reticular pattern on the granular background. The hilar vascular shadows become fuzzy and indistinct and slightly enlarged. Only three showed enlarged hilar nodes, two of them moderate in degree, one rather marked.

"*Stage 3.* Distinct nodules appear uniformly through the lungs, varying from 1 to 5 mm. in diameter, and the appearance now resembles a snow storm. Several in this stage have shown multiple small dark areas between the reticulo-nodular shadows, giving the appearance on a single film resembling the cut surface of a sponge. These could be due to small areas of emphysema. The nodules are evenly distributed throughout both lungs. They do not coalesce, do not calcify or cavitate, and there is no definite linear fibrosis. The hilar shadows are quite fuzzy and indistinct, probably in part at least due to surrounding and overlapping nodulation. Pleural effusions are still absent, but the heart shadows in this stage become slightly larger, and the pulmonary artery may become quite prominent. There is no basal emphysema demonstrable, although one patient's films showed progressive upward displacement of the hila and the interlobal fissure on the right side.

"The terminal picture may be complicated by heart failure (pulmonary congestion, hydrothorax, and cardiac dilatation), but we saw no x-rays in this stage.

"One patient apparently did not go beyond Stage 1 and then showed subsequent clearing but did not return to normal. The granular appearance is still recognizable. One other patient improved roentgenologically after reaching Stage 3 (early). The hilar shadows remain enlarged, and the lung markings are definitely exaggerated, but the nodularity and the granularity have disappeared.

"The roentgenological appearance in the third stage may be closely simulated by sarcoidosis, or lymphangiectatic carcinomatosis, and an occasional case of erythema nodosum with marked pulmonary changes. It is less closely simulated by acute silicosis, miliary tuberculosis, a rare case of diffuse fungus infection, and, occasionally, by the diffuse pneumonitis and miliary atelectasis which may follow an acute virus infection.

"Nothing in our experience simulates the granular appearance in Stage 1.

"The cardiac changes were obviously pre-existent or secondary to the increase in pressure in the pulmonary circulation. One would have expected cyanosis to be reported more constantly. The presence of clubbing in the extremities in only two cases is hard to understand."

Subsequent cases and careful roentgenological "follow-up" on many of the cases included in the above report have changed our original concepts only in minor details. It is now apparent that the latent period may extend beyond three years in some cases. The description of Stage 1 is still characteristic. The incidence of nodular enlargement in the hilar areas has definitely increased. Either closer packing in some areas has simulated it, or there has been actual coalescence of lesions in several cases. This has usually occurred in the upper lobes, and more

Fig. 13. Pulmonary granulomatosis. Late nodular stage, packing of the nodules in the right upper lobe, elevation of the short septum, basilar emphysema, and prominent pulmonary artery.

frequently on the right. It is associated with upward displacement of the short septum and basal emphysema. In 7 cases a small amount of pneumothorax has recently developed but with very little additional respiratory distress. No associated fluid or other pleural involvement was distinguishable roentgenologically, however. As basal emphysema has developed with longer duration of the disease, clubbing of the fingers and cyanosis have also become more frequent clinical findings. A few cases have shown a clearing of the granular and nodular densities, but some residual linear fibrosis is present, and, clinically, there is still evidence of subnormal pulmonary function.

The size of the nodules varies somewhat in individual cases. In a few the original "sand-like" pattern seems to be retained or simulated by much finer nodulation than in others. These patients do not show any greater disability, though usually the incapacity seems greater during Stage 1, with improvement of symptoms in the other stages. It should not be assumed that all cases must progress in these stages, but many do. Many cases show apparent remissions with acute exacerbations accompanied by loss of weight, greater dyspnea, and cough. X-ray examinations during these more acute attacks show evidence of what is believed to represent edema. The patient usually recovers following bed rest and oxygen therapy, and the chest roentgenogram promptly returns to the pattern seen prior to the attack. Those who succumb with this disease usually have cor pulmonale, though some with this complication do improve. The degree of involvement of the lungs, as shown roentgenologically, is not always an indicator of the degree of disability. Two or three patients with well advanced Stage 3 changes are almost symptom-free. These are the exception, however, rather than the rule.

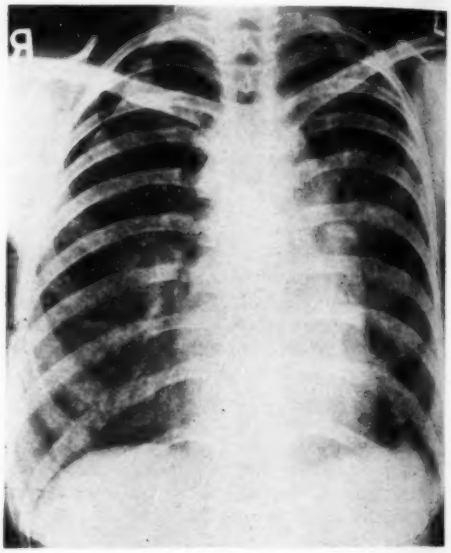


Fig. 14. Pulmonary granulomatosis. Spontaneous pneumothorax on the right.

X-ray examinations of other systems have been consistently negative except for a few cases of urinary calculi.

DIFFERENTIAL DIAGNOSIS

In the differential diagnosis of pulmonary granulomatosis of beryllium workers from other conditions which simulate

its roentgen pattern, one must be guided by occupational history, clinical history, physical findings, and laboratory analyses, as well as the chest roentgenograms. Unfortunately, one cannot rely completely on occupational history in conjunction with x-ray findings, since some workers may have been exposed to other irritants in addition to beryllium. Consideration must also be given to the incidence of any disease in relation to the general population, and this applied to the number of employees. Roentgenologically, the lung changes associated with beryllium exposure have been confused most commonly with pulmonary sarcoidosis, miliary tuberculosis, and silicosis. All of these were originally entertained as diagnoses in the earlier cases.

Pulmonary Sarcoidosis: Pulmonary sarcoidosis is characterized by three manifestations, all of which may be present at the same time, but any one of which may be absent: mediastinal and hilar enlargement, peribronchial fibronodular infiltration, and discrete miliary nodulation. The enlargement of hilar and mediastinal nodes is not so evident or so great in the disease under discussion. Peribronchial fibronodular change is not so apparent, and the discrete nodular infiltration is uniformly distributed from apices to bases. The latter could occur in sarcoidosis, but is uncommon, while in this disease it is the rule rather than the exception. Clinically, of course, there are other differential points.

Miliary Tuberculosis: There are two types of miliary tuberculosis, acute and chronic hematogenous. The clinical course of acute miliary tuberculosis would, of course, differ considerably from that of beryllium (?) granulomatosis, and it is probably safe to say that one would not encounter the very fine "sandy" roentgen pattern throughout both lungs that is characteristic of the latter condition, though the fine nodular response might be confusing. In the chronic hematogenous spread of tuberculosis, the same observation would be true of the x-ray study. In addition, the nodules are less likely to be

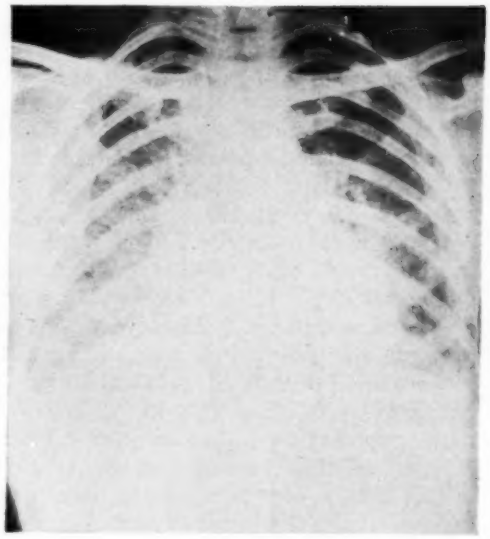


Fig. 15. Atypical case, following exposure to beryllium oxide. Onset nearly four years after exposure.

uniform in size or distribution in this type of tuberculosis, and again, there are clinical factors which aid in differentiation.

Silicosis: Silicosis also produces granulomatous lesions in the lung, but as a rule the distribution is not so uniform or comparable. Some manifestations, however, can simulate the changes in beryllium workers. The occupational history is helpful if the individual has not been exposed to silica. In the roentgenogram, there is no sand-like pattern, and the nodules are more sharply outlined in silicosis.

Some *other pneumoconioses*, such as siderosis, asbestosis, and pulmonary changes in talc workers may also enter the picture.

Among diseases less commonly confused with pulmonary granulomatosis which, at times, require differentiation, several may be listed: (1) Diffuse pulmonary involvement is seen in *erythema nodosum*, two cases of which came to our attention. One patient had been exposed to beryllium; the other had not. One recovered promptly, and both had typical nodules in the skin. (2) *Slowly resolving virus pneumonitis* has proved difficult at times, but

the distribution is not, as a rule, uniform throughout both lungs. Leukopenia is common in virus infections, and there is usually a positive reaction to cold agglutinins. (Both might be obtained in pulmonary granulomatosis, but not likely.) (3) *Heart disease with chronic pulmonary congestion* may simulate the roentgen pattern, but the distribution is not comparable, and other evidence of heart disease usually exists. The hemosiderosis occurring with mitral disease can give a striking similarity, but the differential diagnosis is not difficult, if all factors are considered. (4) One case of *periarteritis with hemorrhagic pneumonitis* seen by the author had some roentgen characteristics of this disease, but there was no history of exposure. (5) There are the several *mycotic infections* to be considered. Histoplasmosis, for example, may produce a miliary pattern in the lung but can usually be differentiated, roentgenologically, clinically, or by laboratory methods. There are, undoubtedly, many other diseases, including the miliary metastases of malignant tumors, Ayerza's disease, Lœffler's syndrome, diffuse adenomatosis of the lung, etc., but the scope of this paper does not permit further discussion.

TREATMENT

Many forms of treatment have been tried, but no specific mode of attack has been found. Rest and good nutrition are indispensable. Chemotherapy, in all its forms, has proved of very little value, except as it may influence secondary infection. One suspected case which seems to follow the same clinical and roentgen pattern has been treated by x-ray, with apparently beneficial results for a time, so far as the roentgenogram is concerned, but with very little clinical improvement. A recent chest film has revealed a recurrence of the original granularity, and more experience will be necessary before accepting this as a possible mode of therapy. In some instances, change of climate has seemed to improve some of the clinical manifestations, but, in most instances, the pulmonary changes as seen roentgenologically have not been improved.

Before concluding, some mention should be made regarding efforts to control this hazard. Considerable difficulty has been experienced in the past in determining the type and degree of exposure, due to the inability of the usual methods of analysis to reveal the presence of minute quantities of the substance in the air, tissues, and fluids of the body. Chemical and crystalline diffraction methods were satisfactory only where relatively large amounts were involved. From the spectrographic study of available postmortem material, it has become evident that amounts in the ratio of 5 micrograms or less per 100 grams of tissue must be identified. Small amounts of beryllium were found in the lung ash spectrographically in 7 cases examined. None was found in the ash of one unexposed control. Spectrography has been the only reliable method for determining such small amounts, and it is hoped that by focusing on the cathode layer, the sensitivity of this method may be increased as much as ten times. This makes it possible to determine the content in the urine, which has hitherto been difficult. It also offers a means of analyzing dust concentrations in the plants and may determine what amount of exposure is safe. In all the cases described in the fluorescent lamp plants, exposure evidently occurred prior to 1943. During this time, the opportunity for exposure was more obvious both as regards the amount of fluorescent powder in the air, on the floor, etc., and the percentage of beryllium which it contained, this being considerably higher than that in the phosphors used from 1943 on. Knowledge of the hazard and better analytical methods have improved control very markedly in these plants. With the more widespread use of beryllium and its compounds, it is obvious, however, that industrial physicians, radiologists, and others must be alert to the possibility. Routine chest roentgenograms instituted in 1943 and a monthly weighing program as screening processes have re-

vealed occasional cases, but in all instances the individual had been exposed prior to 1943.

SUMMARY

An effort has been made to present all phases of a problem which is not completely solved. The recognition of the roentgen manifestations of the pulmonary changes in beryllium workers is most important. A description of these changes and some of the differential diagnoses have been included. Obviously, detailed description and presentation of case histories have had to be omitted. The object of this presentation is to bring to the attention of industrial physicians and radiologists the existence of an occupational hazard.

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SUMARIO

Neumonitis Química o Granulomatosis Pulmonar Difusa Tardías Debidas al Berilio

Desde 1943 han aparecido en los Estados Unidos varias comunicaciones relativas a patología pulmonar en los obreros expuestos al berilio, en particular en relación con la fabricación de lámparas fluorescentes y tubos de neón. Esas alteraciones corresponden a dos formas: aguda y crónica, denominadas, respectivamente, "neumonitis aguda de los obreros en berilio" y "granulomatosis pulmonar de los obreros en berilio." Este trabajo discute la forma crónica.

Una de las características más notables de dicho estado consiste en su tardía iniciación, que puede demorarse hasta seis años después de cesar la exposición. La duración es prolongada, y la separación de la exposición no va seguida de la reposición. Macroscópicamente, las lesiones típicas aparecen en forma de nodulillos blancuzcos difundidos por los lóbulos de los pulmones. La primera manifestación radiográfica es una granulosidad difusa, de aspecto de papel de lija fino, que se extiende hasta la periferia pulmonar y abarca los vértices. El segundo período se caracteriza por un molde reticular difuso sobrepuesto al fondo granular. En el tercer período, obsérvanse uniformemente a través de ambos pulmones, nódulos bien definidos, de 1 a 5 mm. de diámetro, que dan la impresión de una nevada. Creíase primitivamente que los nódulos no se unían, pero a medida que se han ido observando los casos, se ha descubierto fusión en varios. En las zonas hiliares puede presentarse hipertrofia ganglionar. Entre las manifestaciónes clínicas tardías figuran dedos hipocráticos y cianosis.

Algunos enfermos revelan exacerbaciones agudas, con signos roentgenológicos que representan aparentemente edema, yendo el reposo en cama y la oxigenoterapia seguidos de retorno al anterior patrón roentgenológico. En los casos letales, el *cor pulmonale* constituye una característica habitual.

Los principales estados que exigen diferenciación de la granulomatosis pulmonar en los trabajadores en berilio son: sarcoidosis pulmonar, granulia, y silicosis. No se ha encontrado todavía ningún tratamiento específico para la dolencia. El reconocimiento del riesgo ha motivado medidas de control, pero los radiólogos deben tener presente esta posibilidad.

DISCUSSION

(Papers by Pendergrass and Robert; Hatch; Corcoran; Machle; Shaver; Wilson)

Philip Drinker (Boston, Mass.): As an engineer I am tremendously interested in what you roentgenologists do in the way of helping us with diagnosis by getting better case histories and not simply by judging from the films as you see them. We have had too many instances in industry where—perhaps unintentionally—wholly misleading information has been given to the doctor by the patient.

A classical example may be taken from my own specialty in metallurgical plants. Outside of Pittsburgh there is a large smelter where they handle nothing but zinc ores; no lead ores come into the place at all, and the lead that is contained in the zinc is there in traces only. On the factory, however, is a large sign, "St. Joseph Lead Company." Every time anybody from that factory had a stomach ache, it used to be diagnosed as lead poisoning, and it took a lot of explaining to make the doctors realize that, whatever the man had, it was not lead poisoning.

A case recently came to my attention from another smelter, where a man alleged that he had silicosis. I think that in this particular instance the matter will be set straight, since the diagnostic findings, especially in the x-ray picture, are not those of silicosis. Actually the plant is a copper smelter, where the molds in which the copper is poured are given a preliminary wash with a mixture of various calcium salts—calcium phosphate and carbonate predominating. There is no silica at all in the wash. Not a great many years ago, however, there might have been, and the use of such washes in foundries is traditional. It is a matter of only about twelve years since so-called silica washes in foundries have been eliminated, thus avoiding an important source of silicosis.

May I remind you that we engineers and other laymen look to you radiologists for a very difficult decision—an estimate of disability in these cases. I realize that that puts you on the spot in a great many cases, for if you look upon roentgenology as a true science rather than an art, you probably will be a little loath to say that a man is reduced to half or a third of his working capacity. But if you don't accept this responsibility, then lay people must, and that is certainly to be avoided.

The last person who should fix the percentage disability is the man who hears the case, the Industrial Commissioner. Whatever his qualifications, political or otherwise, they most certainly are not medical. Yet, if you refuse to fix the percentage of disability, through your medical wisdom and good medical common sense, then the Commissioner is going to have to do it.

We like to simplify these things if we can, but we are thoroughly mindful of the effects of time, duration of exposure, and also of infection. We feel that the medical profession has contributed greatly to the elimination or reduction of silicosis by emphasizing the importance of tuberculosis. I know of mining communities today in which silicosis is no longer a significant hazard where, as short a time ago as fifteen years, it was most serious. In the particular place which I have in mind, engineers have contributed in some measure, but the medical and public health workers contributed a good deal more by getting the tuberculous workers out of the mines entirely. I was especially interested, therefore, in what Dr. Corcoran had to say about the comparative safety—or at least assurance of a reasonably long period of work—if infectious processes were excluded.

As to beryllium, it is a source of great regret to us engineers that we still have no reasonable idea how clean the air has to be. Whereas you people may be embarrassed by trying to guess at a man's disability, we are equally embarrassed by having to go to an employer and say that we expect him to install dust control and that, if he will do exactly what we say, we will tell him in about ten years whether he did it right or not. The general motto is: "If the place is dusty, it's too dusty."

I was rather disappointed that Dr. Shaver didn't come out and say what he thinks is the cause of the lung condition that he showed. In his table of analyses he gives exposures to a fume that, as I remember his figure, is around 50 per cent Al_2O_3 and something on the order of 35 per cent SiO_2, the bulk being of the extremely small particle size. If it's fair to bet on such a thing, my money is certainly on the SiO_2 and not on the Al_2O_3. But it seems to me that in this particular case, the incriminating agent could be proved by animal experimentation and perhaps on a basis that is a lot simpler than going back to the actual plant process.

Lowrey Davenport, M.D. (Boston, Mass.): As a chest physician I have very little to add to the admirable presentation of the diagnostic criteria, from the roentgenological standpoint, and the pathogenesis of these various industrial diseases. But much has been made this afternoon by each succeeding speaker of the teamwork necessary between the roentgenologist and those who study these conditions from the clinical side. There are hazards involved in this, and I should like to point out some of the difficulties that confront those of us who are engaged in trying to

track down the clinical significance of the x-ray shadows and to interpret them in the light of careful occupational histories.

I think we are all well aware how much more definite first-stage silicosis looks after we have a history of definite exposure to silica. The x-ray shadows are much more apparent to all of us who study the films after we know that exposure has taken place. Also, we know that the chronic productive nodular type of tuberculosis looks less and less like nodular silicosis when the sputum is positive and when the patient is a female without any industrial exposure whatever. Conversely, once an official x-ray interpretation has raised the question of industrial disease and labeled a patient as having a presumptive case of pneumoconiosis, it is extraordinary how dusty many occupations look when they are investigated.

It is almost impossible, then, to absolve many industries from a possible causative dust factor once a case is officially declared to be a presumptive pneumoconiosis. That has been particularly troublesome in mass surveys, where the temptation, in reading x-ray films without any history, is to make a definite diagnosis on a single film. We have got around that in some of the institutions in the State by leaving the diagnosis open, describing the pattern of the disease and then inquiring into the occupational history, so as not to confuse the issue from the very beginning. Once the issue of pneumoconiosis has been raised, because of the angle of compensation in this State and in most States, it is extraordinarily difficult to get at the actual facts of the case.

Massachusetts, in contrast to Pennsylvania as cited by Dr. Corcoran, (wisely, I think) has not laid down any definite time interval or definite regulations for any of these claims, saying that each shall be judged on its own merits. One case cited by Dr. Machle bears out the question of time interval in the development of silicosis. In a factory here in Massachusetts, that was making soap powder in about 1930, using a considerable quantity of alkali mixed with silica, there was a case on record in which advanced silicosis developed within fourteen months. I have within this past year seen an individual from this same plant who was completely absolved of disease by repeated x-ray examinations in the early 1930's. In 1933 he got a job as a bartender, where he remained for the next ten years, finally showing up with advanced silicosis developing years after the original exposure.

These 2 examples—one developing within fourteen months and one developing after ten or twelve years—presumably with the same exposure, serve to emphasize that these cases must be considered on their individual merits. I feel that we cannot stress too strongly that the differential diagnosis must depend on correlation of the industrial background and the history of exposure, with careful reference to time factors, knowing that in the odd case all rules fail.

Much has been said about the presence or absence of free silica, and it is well to make an additional comment: that there are certain types of free silica, particularly in modern abrasives and grinding wheels, which do not cause silicosis. A modern grinding wheel, made up of either aluminum oxide or aluminum carbide, may be bonded with silicates, and the bonding substance may contain certain amounts of free silica. Because of the vitreous bond of these wheels, the free silica does not act as the definite irritating factor that silica does in certain other situations.

Even with careful occupational histories and a knowledge of the various types of silica to which an individual is exposed, we feel—and I think the Commonwealth of Massachusetts is right in insisting—that each case should be judged individually on its own merits and on the factors in the particular situation.

Dr. Pendergrass: I would like to have Dr. Davenport comment on a statement made by Dr. Drinker that a part of the radiologist's job is to determine the amount of disability.

Dr. Davenport: I'm afraid I cannot agree with Professor Drinker that it is the roentgenologist's job to comment on the question of disability, nor can I agree with some of the other speakers who say that silicosis in and of itself does not produce a definite disability.

We are faced in many situations with a man who is approaching physiological old age, who, either consciously or subconsciously, because of compensation factors, is exaggerating his symptoms. It is very difficult to decide in these cases about lowered physiological reserve. I think all of us are probably given enough lung to be marathon runners if we wanted to train for it, so percentage disability is an extremely variable thing.

In trying to evaluate disability, we are accustomed to accept the patient's symptomatology at its face value, given definite fibrotic changes in the lung, for I know of no really objective signs which can definitely exclude the possibility of impaired lung function in any stage of silicosis.

In answer specifically to your question, Dr. Pendergrass, I should say that it is not the province of the roentgenologist to determine the question of disability.

Harriet L. Hardy, M.D. (Boston, Mass.): I am like Dr. Wilson; I'd like to scrap a bit about the nomenclature. I hope the time is at hand when we can start calling the disease which he described beryllium poisoning. The chemical engineers and physiologists haven't quite got us there yet. I feel strongly that it is like lead poisoning, *i.e.*, it is a systemic condition. At autopsy, lesions

are found in the liver, spleen, and the nodes, and now that spectrographic analysis is beginning to be used more extensively we are finding beryllium in other viscera.

To go back to our clinical experience, there are a great many biochemical changes of the greatest interest that we haven't the slightest idea how to interpret. There is high blood calcium in a few cases, in 2 instances correlated with the passage of a kidney stone. There is pretty much always an elevation in the total protein when the patients are seriously ill—when the disease is more what we call the malignant type—and on electrocardiographic study, a unique pattern is obtained, that no one has ever seen before. In other words, there are a great many phenomena in the biochemistry of the body that suggest that this is not simply an inhalation of material that is in some fashion held in the alveolar walls and then later on leads to the curious picture that you have heard described.

Another thing that has led me to feel that beryllium poisoning will ultimately be the best designation for this condition is the opportunity that I have had to study the case of a negro worker who was exposed to beryllium in such a way as to get an acute chemical pneumonitis. He was taken out of the environment and got well. Then he was put back in the same environment and got sick again, with the x-ray pattern such as you saw this afternoon. So he was again taken off and this time was put on a job as a truck-driver, quite away from the beryllium industry. Without any further exposure there developed a clinical picture of what we have been calling delayed chemical pneumonitis, and death ensued. At autopsy the tissues were found to contain the granulomatous lesions that we consider characteristic. I would conclude from this that the acute and chronic forms belong together; that they can merge, depending on the character of the exposure, and doubtless difficulties within the individual that make the particular case clinically what it is.

Another very disturbing, very fascinating problem is that people who had never gone into the factory but lived near the place where beryllium compounds were handled have become ill and have died of this disease. I have called them "neighbor cases." I know of 4 such cases with 2 autopsies, and the pathologists are not able to distinguish them from the worker cases. This aspect is a public health problem and now that the industry is aware of the hazardous nature of the material it is doubtful if many more such cases will be seen. The Russians reported this same phenomenon in 1933. Watchmen who never went into the plant where beryllium was being handled but worked some distance away showed the same clinical picture as the factory workers.

One other thing I should like to bring to your attention. Dr. Gardner produced osteogenic sarcoma by putting into the veins and the tracheas of rabbits material to which workers were exposed in the fluorescent-lamp-manufacturing industry. That may be a laboratory stunt; we may never find such a thing in human beings—we certainly hope not—but it is too dramatic not to mention in thinking in terms of the delay in onset, in terms of the blood calcium figures that we don't know how to interpret. Is there a possibility that the bones are storing this material and that we may be so unfortunate as to see, after this war, some such fantastic phenomena as we did in radium dial painters after the last war?

Dr. Pendergrass: This symposium is now open for discussion. Are there any questions?

Question: Is silicon carbide causing as much silicosis now as reported some time ago?

Dr. Pendergrass: Will someone answer that question when closing the discussion?

Another question that has been handed to me for Dr. Corcoran: Do you believe a definite diagnosis of prenodular silicosis or anthracosilicosis can be made without following the case to later stages and then using hindsight?

You will recall that when Dr. Corcoran made his presentation he emphasized the importance of the size of peribronchial and perivascular shadows. I am glad that he brought that up because I'd like to have him elaborate on that point when he closes his discussion.

We have taken the position that as radiologists we cannot make any such interpretation. I have a roentgenogram of an excised pair of lungs. Before these lungs were removed from the chest, the pulmonary vessels on the right were ligated and they are filled with blood. On the other side, the blood was allowed to drain out and then the inflated lungs were taken out of the chest cavity and the roentgenogram was made. One sees a tremendous shadow from the vascular tree alone. One does not see the bronchial tree even in the excised lungs.

With the aid of a cardichron, we have demonstrated to our own satisfaction that there is a tremendous difference between the size of the vascular markings in systole and in diastole, the shadows being larger in systole and smaller in diastole. Consequently, in our own department we expose all of our films in diastolic phase of the cardiac cycle so that one can compare the roentgenograms made at different times. In our own experience we have not been able to rely on our opinion as to whether or not there is an exaggeration of these shadows produced by pneumoconiosis.

Therefore, I personally would like to see us, as radiologists, stick to those shadows that we can agree upon today, that we can agree upon six

months from now, or that we can agree upon twenty-five years from now. In other words, I would like to see us confine our diagnoses in pneumoconiosis to those shadows that do not change with the cardiac cycle and with slight changes in the ventilation of the lungs or the amount of blood that is in the vessels.

I believe we can agree on nodulation. What the nodulation is due to is another thing. It may be a benign type of lesion; it may be a clinical condition that has no reference to pneumoconiosis, or it may be silicosis. I should therefore like to have Dr. Corcoran, in his closing discussion, comment on whether one should make a diagnosis of silicosis in the absence of nodulation.

I will call on Dr. Robert to close the discussion on his paper.

Agrippa G. Robert, M.D. (*closing*): I am very glad that Dr. Hatch called attention to the pitfalls that may exist in the evaluation of an occupational history. Certainly they are present and they are often very difficult of proper appraisal.

The fact remains, however, that so many other conditions, which must be considered in the differential diagnosis of silicosis, produce nodulation that we must have something in the way of an occupational history before making the diagnosis. From the films alone I do not think that we are justified in making an unequivocal statement that nodulation seen in a given case is necessarily silicotic in origin.

Also his discussion of iron oxide as a possible factor in the production of nodulation is one that must receive consideration. I believe that Collis, a number of years ago, raised the question in England, as to whether some of the shadows seen in cases of silicosis might not be the result of the inhalation of radiopaque material. In our studies of iron miners, however, Dr. Gardner was able—in those cases coming to autopsy—to identify as silicotic the roentgenographically demonstrable nodulation.

In regard to Dr. Corcoran's paper, there is a question that I should like to ask. Dr. Pendergrass has stressed the fact that we do not make the diagnosis of silicosis unless we can see nodulation in the lungs. I was interested in the statement that tuberculosis is common after fifty in these individuals and is more common in cases showing conglomerate fibrosis.

I wonder if Dr. Corcoran feels—as we do—that the conglomerate fibrosis resulted from preexisting infection (usually tuberculous) and that infection which becomes manifest after the age of fifty most commonly represents a reactivation of an old focus, the existence of which is indicated by the very presence of conglomerate nodulation.

Dr. Davenport stated that we cannot estimate the disability of an individual from the film alone. I should like to express my hearty agreement. I believe, however, that we now have enough studies on ventilatory capacities in individuals with silicosis and individuals comparable as to age, height, weight, muscular development, etc., to say that some of the disability of which these people complain is the result of physiological deterioration with age. It is very difficult to find any difference between control individuals studied as to their ventilatory capacities and those showing a simple discrete nodulation which has developed over a long period of time.

Theodore Hatch (*closing*): I would like particularly, to echo one point that Dr. Davenport emphasized—the danger that comes from labeling an industry as silicosis-producing from a limited number of film readings. To illustrate, compensation tables in one State list fourteen silicosis claims allowed among grinders, making this, officially, a silicosis-producing operation.

Now, grinding with a modern synthetic abrasive wheel will *not* produce silicosis in itself, since there is no significant free silica present. This applies to silicon carbide, about which one gentleman inquired. The source of the silicosis in these reported cases must be found elsewhere than in the grinding wheel—yet the record itself labels grinding as the hazardous operation.

Again, I should like to refer to the influence of iron oxide. In grinding operations on iron and steel, the outstanding constituent of the dust is iron oxide. In view of the established fact that iron oxide in the lungs can produce x-ray shadows, not unlike those of silicosis, in its own right, certainly it is proper to question an x-ray diagnosis of silicosis in a metal grinder.

I do not wish to give the impression that the etiology of silicosis is so uncertain that we cannot properly use occupational histories. However, I believe there has been too loose interpretation of occupational histories based upon some generalized rules that do not necessarily fit all the cases.

We need more systematic studies to extend our knowledge of the etiology of the disease so that, in the future, occupational histories can be interpreted with greater certainty.

William J. Corcoran, M.D. (*closing*): If we have a second stage of silicosis—anthraco-silicosis—and everybody agrees to that, then we certainly must have a first stage. We have roentgenograms of patients (and Dr. Pendergrass has) that go beyond twenty-five years. If we take a chest that has nodules in it—diffuse nodules, discrete—we would find, if we had roentgenograms of that same patient for several years back, that those nodules would not yet have appeared. In succeeding years we would begin to see these nodules. This occurs in the majority of cases. Prior to nodule formation, as you know, the appearance is one of peribronchial, perivascular

linear fibrosis, and, when no nodules are yet apparent, we term that the first stage.

As we stated in our paper, we do not believe that a diagnosis of first-stage anthraco-silicosis can be made with any degree of assurance on the roentgenogram, but when we have profuse discrete nodulation throughout both lungs, quite symmetrical on the two sides, the diagnosis is certainly consistent with the occupation of the person, and in my opinion nodular anthraco-silicosis is a justifiable diagnosis. This is the second stage.

When those nodules coalesce and there are conglomerate masses in the lungs, the condition is called third-stage. We distinguish between early, middle, and advanced third-stage silicosis.

As to the hilum shadows that Dr. Pendergrass talks about, I think one of the main things is their increase in density, their shifting, of course, and their measurements.

I don't know whether I have answered the question or not.

Dr. Pendergrass: No, you have not, Dr. Corcoran. I think you have got in deeper. You have intimated—and I don't believe you mean to do that—that if you get a first-stage silicosis you are likely to get a second- and third-stage silicosis. You have intimated that it is not possible to have massive shadows in the lung without having the nodulation that can be seen on the roentgenogram.

Now let's be practical about this thing. One cannot see a nodule in the lung unless it measures at least 3 mm. in diameter. You can see it microscopically but you cannot see it on the roentgenogram. There can be any number of nodules on the peripheral portions of the lung—some measuring as much as a centimeter—which cannot be seen in a roentgenogram.

We are talking about radiological interpretation. We have an important role to fill in this program. We are the ones that are muddying the water for the engineers and for the clinicians, for the employee and the employer, and therefore I am anxious that we as radiologists accept that responsibility and not become too theoretical about this whole thing.

I hate to see this term "stage" used, because the Compensation Referee and the lay group that decide these things think that if we have a "first-stage" silicosis we are going to ultimately get a second stage and a third stage.

Dr. Corcoran has in his files, I am sure, records of patients with nodulation throughout the lungs who ten, fifteen, and twenty-five years later do not show the slightest change.

We also know from experimental evidence that one can get fibrosis around these silica nodules and they will just stay there; there won't be any progression. Dr. Robert called attention to that today. We also know that if you get deposits of silica in the hilar lymph nodes, they don't necessarily enlarge. They may get large in the beginning but if the condition is allowed to go on and develop, they contract instead of getting larger.

This is the sort of thing, Dr. Corcoran, that I want you to leave in the minds of this group. I know that you and I agree, but we can't talk loosely because the matter is of such importance to the employee and the employer and to those people like the engineers who are trying to help us.

Dr. Corcoran: Well, Dr. Pendergrass, I have lived with these people, and anthraco-silicosis sufficient to produce changes in the lungs in the so-called perihilar, peribronchial, perivascular areas, going on to diffuse, discrete nodulation throughout both lungs, will, if the patient remains in the hazard, in most instances go on to conglomeration.

The rate of progression—and I so stated in my paper—when the patient is removed completely from the hazard, naturally is much slower, and whether or not it goes on to a very advanced third stage depends on the stage at the time of removal from the hazard. Progression will not occur in all stages.

I feel that we have to say "first stage." If we are going to say second, we must say first. I have roentgenograms of men who were exposed from eight to ten years, in whom the condition did not progress to what I call a second stage, where the nodules appear discretely.

To use the word "stages" has advantages and disadvantages.

Dr. Davenport said that he could not agree with what some of the speakers here emphasized, one after the other, that anthraco-silicosis alone could not produce a disability. The law under which we operate in the State of Pennsylvania states that the man must be totally disabled from anthraco-silicosis solely, the only exception allowed being active pulmonary tuberculosis. If a claimant has active tuberculosis with silicosis, regardless of the stage of silicosis, at the time that he presents himself for hearing, there is an automatic award, provided the legal requirements as to the Act are met.

I don't split a man's lungs from his heart, and I don't take a man's lungs from his thoracic cage, but the law apparently does. If a man with a late third-stage anthraco-silicosis has less than an inch of expansion, it is the result, in my opinion, of his silicosis. I believe that a heart does suffer right strain in late stages of silicosis in some cases; I believe that tuberculosis is more common after the age of fifty in silicotics.

Dr. Pendergrass feels that I have intimated to the group here that if you get a first-stage silicosis you are likely to get a second and a third stage. I certainly do not wish to convey that impression, but if a man is in a silica hazard and remains there for a long period of time, he is *likely* to go on to a third-stage silicosis, though not all of the workers

do. We have all seen men who have worked for as many as from thirty to forty years in a silica hazard, who still do not show changes on the roentgenogram indicative of third-stage silicosis. I also wish to state that I agree with Dr. Pendergrass that we may see chests with large conglomerate masses in each lung with very little evidence of nodule formation.

My object in presenting this paper is to convey to you what happens in the average case or in the majority of cases. There are exceptions, of course, to the rule, and there are many exceptions to much that we can say about anthraco-silicosis.

Willard Machle, M. D. (*closing*): I just want to add one word that deals not with my subject but with the matter of exposure. As you know, exposure implies not only that the patient is where a material is being used but also that the material is of proper size distribution, is present in the air in adequate quantity, and is capable of getting into the body.

With respect to the so-called "neighborhood" cases of beryllium granulomatosis, they came about, I believe, not because of unusual susceptibility to the material, but actually as a result of significant exposure. One has seen cases of fluoride intoxication in animals twelve miles from the plant source, while animals on the intervening farms closer to the source have no exposure and no fluorosis. It was only after investigation of the effluent from the plant that it was found that local meteorological conditions were such that the fluorides drifted away from the plant and settled miles away because of local terrain and precipitation, leaving the intervening areas free.

Correspondingly, one has seen cases of silicosis arising in a candy factory, the cases occurring in individuals whose job was mainly to sharpen the knives and spatulas on sandstone grinding wheels.

Accordingly, the business of interpreting exposure—and this goes on infinitely with respect to silica, lead, etc.—can only be done adequately when you yourself, or an engineer, goes into the place of employment, scrutinizes it and evaluates the exposure with respect to distribution, particle size, solubility, and kinds of materials involved.

C. G. Shaver, M.D. (*closing*): Professor Drinker would like to make a bet with me in regard to the cause of this disease in workers in alumina abrasives. Well, in the first place, American money comes to our side very easily but it is very difficult to get Canadian money back to this side, so it would be quite unfair.

We thought at the onset that silica was the causative factor. Then, as we went along, Professor Boyd at the University of Toronto studied some of the pathological slides and he thought they showed an atypical silicosis. He may have been influenced somewhat by the amount of silica present in the fume and in the lung ash.

During the latter part of the war we obtained some literature from Germany (reported by Godehard Goralewski) on men who had been aluminum punchers, and these reports definitely blamed alumina as the cause of the disease occurring in that group of men, and from what we can gather in the literature the cases shown to-day have a similarity. I mean it is the same type of diffuse granulation associated with pneumothorax. We haven't, however, been able to get from the Germans details as to the exact work or any other materials that may have been mixed up with the alumina, so that in this regard we aren't at all sure. Then we felt that if silica were responsible, we would probably find tuberculosis developing and, as I stated today, we found one case.

Experimental work is being done at the University of Toronto. Animals are being exposed to the fume divided into its separate components, but so far they haven't demonstrated the exact cause of the disease. In work carried on at Saranac Lake under the direction of the late Dr. Gardner, it was possible to reproduce the disease in animals from the fume, but this has not given us any specific cause.

Professor Drinker informs me that we don't have to manufacture the fume, it can be manufactured on a commercial basis and used in that manner. Perhaps that will be the solution.

I was very glad that Dr. Davenport brought out the point that the finished product of this material did not produce disease, and I would like to add that this has been our experience.

Philip Drinker: As to the question of disability and who is responsible for saying what disability is, I think Dr. Davenport misinterpreted what I said, perhaps because I didn't say it well.

My point is that if you gentlemen do not say what a man's disability is when these cases come to court, then the court will say it, and the court, manifestly, is not so well qualified as you are. I don't say it's your job, perhaps it isn't; perhaps it's a physiologist's job—but we may as well be realistic about this. I have been concerned in many of these cases myself and I know many of you have. The persons on whom they rely medically are the roentgenologist and the chest expert and not anybody else, and I think it is they who should say what kind of work the man is good for.

Penile Carcinoma

A Review of 43 Cases Treated at Bellevue Hospital During the Past Twenty-five Years[1]

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DURING THE COURSE of the past twenty-five years, 43 cases of penile carcinoma were seen in the Radiation Therapy Department of Bellevue Hospital. This number for statistical purposes is small but the series is as large as most reported in the English literature and constitutes an addition to the present comparative lack of material on the subject.

INCIDENCE

While cancer of the penis constitutes but 2 to 5 per cent of all malignant lesions of the skin in males in the United States, the frequency among Hindus and Chinese is 10 and 18 per cent respectively, and the disease accounts for 30 to 40 per cent of all male cancers in the Far East. Cancer of the penis is quite rare among Moslems, who practise ritual circumcision at the age of thirteen, and is practically unknown in Jews, who perform this rite on the eighth postnatal day. Dean, however, cites a case of penile carcinoma in a 66-year old Jew who had cauterization of a venereal lesion at the age of sixteen. The racial and religious distribution in our series was as follows:

TABLE I: RACIAL AND RELIGIOUS DISTRIBUTION

White	35
Negro	7
Chinese	1
Catholic	10
Protestant	10
Jewish	0
Not recorded	23

AGE

The average age at onset of symptoms was forty-two years, the largest number of cases, 14, occurring in the sixth decade. The youngest patient was twenty-four, the oldest seventy-seven. Table II shows the age grouping.

TABLE II: AGE INCIDENCE

20–29 years	1
30–39 years	6
40–49 years	6
50–59 years	14
60–69 years	11
70–79 years	5

ETIOLOGY

Melicow *et al.* in discussing the etiology of penile lesions, note the following "precancerous" conditions: leukoplakia, erythroplasia of Queyrat, Paget's and Bowen's diseases. These authors present an excellent clinco-pathological chart which sets forth the differential diagnostic features of these diseases. There was only one intra-epithelial carcinoma in our series.

That phimosis with the retention of smegma plays an important role in the etiology of penile cancer is adequately established by Barney, Dean, and Melicow, who placed the incidence of that condition at 85 per cent, 74 per cent, and 50 per cent respectively. Phimosis or paraphimosis occurred in 52 per cent of our cases. The inspissated smegma is responsible for a mechanical irritation, and the trapped fatty acids produce a chemical change. The early lesions, whether ulcers or nodules, are hidden in the preputial sulcus, and are often erroneously regarded as venereal sores. Such factors account in part for the long delay in procuring proper medical attention, thus maintaining the incidence of early lesions at a deplorably low level.

Signs of syphilis, old or coexisting with cancer of the penis, were found by Wickham and Dauvilliers in 80 per cent of 45 cases. This is a considerably higher in-

[1] From the Radiation Therapy Department, Bellevue Hospital, Dr. Ira I. Kaplan, Director. Accepted for publication in July 1947.

cidence than that reported in the current American literature, namely, 30 to 40 per cent. Five of our series had a syphilitic history; 13 denied such antecedent disease, but in 7 of these the serologic test for syphilis was positive, bringing the incidence up to 29 per cent. In 12 additional cases there was no history or laboratory evidence of syphilis. Sauer and Leighton state there is a close association between syphilis and carcinoma. They noted that the average age for cancer in patients with a previous syphilitic infection was 41, whereas in the others it was 62 years.

SITE OF PRIMARY LESION

Nine of our patients had had a penectomy at another institution with no operative data obtainable, or on admission to Bellevue Hospital the lesion was so extensive as to preclude judgment of the initial site. In the remaining 34 the origin was as follows: in the glans 12, coronal sulcus 7, shaft 7, prepuce 4, unrecorded 4. In 22 men there was either initial or subsequent involvement of the prepuce by a benign or malignant process.

METASTASES

According to most authors, metastasis to the superficial and deep inguinal lymph nodes occurs in 60 to 85 per cent of cases, while distant metastases are rare. The mode of spread, by extension or embolism, is through the dorsal lymphatics of the penis, the internal saphenous and femoral veins, the iliac vessels, and the vertebral system of veins as demonstrated by Batson. Abdominal visceral metastases are reported by Barney in 15 per cent of his cases. Ormond cites a case with pathological fracture of the femur. No distant metastases were found in our group, but 70 per cent first presented themselves with involvement of the inguinal nodes; in 70 per cent the involvement was bilateral.

PATHOLOGY

As the majority of patients admitted to our service had had previous surgical intervention, or presented rather far advanced disease, it was difficult to ascertain from the records whether the initial lesion was ulcerated or appeared as a nodular growth. It may be stated, however, that most penile carcinomas are ulcerated when first seen; a few present a papillary growth or an area of induration. Histologically our cases were as follows: squamous-cell carcinoma, 33; basal-cell carcinoma, 1; intra-epithelial carcinoma, 1. In 8 the histologic nature was unknown.

Although there were 8 cases without recorded pathological confirmation, they are included in this review because they were referred to the clinic with a diagnosis of cancer and this was borne out by the clinical appearance of the lesion. The treatment of these cases was based on the clinical findings. Six additional cases were not included in this analysis because there was no adequate proof of malignancy, or because biopsy revealed a benign condition.

There was no attempt to grade the lesions according to Broders' criteria.

TREATMENT

No standard method of treatment was possible because a large number of the patients reported to the Radiation Therapy Department (1) after surgery or irradiation had been administered at another institution; (2) following some surgical procedure in the Genito-Urinary Department of Bellevue Hospital; (3) upon request of the Dermatological Service or the Venereal Disease Clinic.

The methods employed and the number of cases in each group are as follows:

I. Surgery Alone: 1 case. This patient had extensive recurrence following total penectomy and bilateral inguinal node dissection. Only custodial care was recommended.

II. Surgery and Radiation: 29 cases
  A. Total penectomy with:
    1. Preoperative irradiation..... 2
    2. Pre- and postoperative irradiation..... 1
    3. Postoperative irradiation..... 13

B. Total penectomy and inguinal node dissection with:
   1. Pre- and postoperative irradiation..... 2
   2. Postoperative irradiation..... 2

C. Partial penectomy (or excision of lesion) with:
   1. Pre- and postoperative irradiation..... 1
   2. Postoperative irradiation..... 7

D. Partial penectomy and inguinal node dissection with:
   1. Postoperative irradiation..... 1

III. Radiation therapy alone: 13 cases
   A. X-rays..... 4
   B. Radium..... 1
   C. X-rays and radium..... 8

Note: In 8 of the cases the initial procedure was either circumcision or dorsal-slit.

Because of the volume of cases seen by us after treatment elsewhere, our material was insufficient to provide significant data. From a review of our cases, however, and those in the literature, an outline for therapy is suggested without claiming originality or implying that it is the best approach.

I. *General Considerations:* Circumcision should be done in all cases. When indicated, vigorous antisyphilitic therapy is advocated either before or simultaneously with irradiation. Supportive measures, such as transfusions and supplementary vitamin administration, should be given as necessary.

II. *Proposed Methods: A. If the lesion is less than 2 cm. in diameter and non-infiltrating:* (1) Medium-voltage x-ray therapy (125 kv.; 0.25 mm. Cu and 1.0 mm. Al filter; h.v.l. 0.4 mm. Cu; 30 cm. target-skin distance; portal size to include tissue 1 cm. around the lesion) with a total dose to the tumor of 4,000 to 6,000 r, or (2) a radium mold 1 cm. thick, with radium tubes sufficient to cover the involved area, giving a dose to the tumor of 6,000 r (gamma).

B. If ulceration with infiltration is present: (1) High-voltage x-ray therapy to the inguinal areas (200 kv.; 0.5 mm. Cu and 1.0 mm. Al filter; h.v.l. 0.9 mm. Cu; 50 cm. target-skin distance; portal size to cover the inguinal regions) for a total tissue dose of 1,800 to 2,400 r to each side, followed by application of (2) a radium mold to cover the penile lesion, as above noted.

C. If the corpora cavernosa are involved: (1) Preoperative high-voltage x-ray therapy to the inguinal areas for a total dose to the tissues of 1,800–2,400 r; (2) penectomy and bilateral inguinal node dissection, and (3) postoperative high-voltage x-ray therapy to the perineum, repeating the preoperative dose. Treatment to the inguinal areas is given only if there is histologic evidence of carcinoma in the excised nodes.

D. If the inguinal nodes are involved but not fixed: (1) Preoperative high-voltage x-ray therapy to the inguinal regions, or radium pack therapy, the unit containing 5 gm. of radium filtered through 2.0 mm. Pt equivalent, covering an 8 × 10-cm. field and applied at a distance of 6 cm., for 30,000 to 40,000 mg. hr. This is followed by (2) penectomy, orchiectomy, resection of the scrotum, and bilateral inguinal node dissection, with (3) postoperative high-voltage x-ray therapy to the perineum for a dose of 1,800 to 2,400 r. The inguinal areas are treated only if dissection was incomplete.

E. If the inguinal nodes are fixed, we advise radium pack therapy, as it seems to be most effective. Treatment is usually limited to palliative measures. If the nodes become resectable, plan D is followed.

F. Recurrences are treated according to plan E.

RESULTS

In attempting to analyze our results, we were handicapped by the limited number of cases followed. Twenty-four patients were

lost sight of within the first year after their registration at the Clinic. Further discussion will therefore be restricted to the remaining 19 patients. Of these, 7 are alive and free of disease, 5 are alive with disease, and 7 are dead.

Of the 7 patients who are alive without disease, all were treated by a combination of surgery and irradiation. In 5 a partial penectomy was done and in 2 a total penectomy. One of the latter had also bilateral inguinal node dissection. Radiation therapy was administered postoperatively in 5 cases; both preoperatively and postoperatively in 2. The follow-up periods in this group were: one month, three months (2 cases), eleven months, two years and four months, three years, and five years.

Three of the 5 patients alive with disease were treated by total penectomy and postoperative x-ray therapy; the other 2 were treated with x-rays and radium. The observation periods in this group are thirteen months, fourteen months, two years, two years and four months, and twelve years.

Because of the unusual twelve-year survival, some remarks about this case are indicated. The patient was a Negro who had had an amputation of the penis for carcinoma at the age of twenty-seven. He was asymptomatic for the next eleven years, at the end of which time he reentered the hospital because of dysuria and hematuria. At that time an orchiectomy and resection of the penile stump were performed, and the pathologist reported: "Keratin pearls in a highly vascularized granulation tissue. *Diagnosis:* Squamous-cell carcinoma." One year later, the patient was re-admitted to the Genito-Urinary Ward because of recurrence of dysuria. Examination revealed "a purulent drainage from the postoperative site; a large indurated area involving the perineum and symphysis; a few hard, painless, freely movable nodules palpable in both groins." The patient received high-voltage x-ray therapy for a total of 2 × 2,400 r (in air) to a right and left supra-pubic field, followed by a total of 1,000 r (in air) to a perineal port. He was subsequently discharged to another hospital, and the final result is unknown.

Only one of the 7 deaths was attributable to the cancer itself, as may be seen from a glance at Table III.

TABLE III: CAUSES OF DEATH

Cause of Death	*Duration of Illness*
Anesthesia, 1	4 months
Suicide, 1	1 year, 3 months
Tuberculosis, 1	1 year, 10 months
Pneumonia, 2	1 year, 5 months; 2 years, 1 month
Carcinoma, 1	8 months
Unknown, 1	2 years, 10 months

The average duration from onset of symptoms to death was eighteen months; average from the beginning of treatment to death was ten months.

SUMMARY AND CONCLUSION

1. Forty-three cases of penile carcinoma treated at Bellevue Hospital during the past twenty-five years are reported.
2. Circumcision at an early age seems to offer protection against the development of penile carcinoma.
3. Cancer of the penis is frequent among syphilitics.
4. A method of treatment for various clinical stages of penile carcinoma is proposed. Early lesions may be treated with x-rays and/or radium; a combination of surgery and radiation therapy is preferred for the advanced cases.

NOTE: The author wishes to express his sincere thanks to Dr. Ira I. Kaplan and Dr. Rieva Rosh for their invaluable guidance in the preparation of this paper.

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SUMARIO

Carcinoma del Pene: Repaso de 43 Casos Tratados en el Hospital Bellevue Durante los Ultimos 25 Años

Comunícanse 43 casos de carcinoma peniano tratados en el Hospital Bellevue (Nueva York) durante los últimos 25 años. De los enfermos, 35 eran blancos, 7 negros y uno chino. En 29 por ciento había signos de sífilis anterior o actual. En ningún caso se descubrieron metástasis remotas, pero 70 por ciento mostraban invasión de los ganglios inguinales cuando se presentaron para tratamiento. La serie comprendía 33 carcinomas escamocelulares, 1 carcinoma basocelular y 1 carcinoma intraepitelial; 8 casos no fueron estudiados histológicamente

Como muchos de los enfermos habían recibido tratamiento antes en otra parte, no pudo aplicarse ningún método terapéutico fijo. En 29 casos se combinaron la cirugía y la irradiación; 13 recibieron únicamente radiación (rayos X, radio, o ambos); 1 enfermo con una recurrencia extensa fué tratado exclusivamente con la cirugía. A 24 de los enfermos se les perdió de vista en término de un año. Al preparar esta comunicación 7 de los 19 restantes se hallaban vivos sin signos de la enfermedad, uno por cinco años y los demás por períodos más cortos; 5 se hallaban vivos pero aun enfermos, uno a los 12 años de amputarle el pene; y 7 habían muerto en un promedio de 10 meses después del tratamiento.

Bosquéjase un plan de tratamiento para las varias etapas clínicas del cáncer del pene. Las lesiones tempranas pueden ser tratadas con los rayos X o el radio; para los casos avanzados prefiérese una combinación de cirugía y radioterapia.

Studies of the Circulation by Roentgencinematography[1]

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THE CIRCULATION of blood occurs under the regulation of definite physical laws. Their clear statement has proved difficult, however, owing to the facts that the vessels divide, that the elasticity and resistance vary in different parts of the circuit, and that a pulsating and not a constant flow exists in the distributing portions. Nevertheless, a number of fundamental physical laws can be derived from simple hydraulic experiments, in which the forces are kept in dynamic equilibrium. These are useful in crystallizing preliminary conceptions, and in understanding the principles utilized in designing apparatus for investigating the circulation. It must be kept in mind, however, that many are only approximations not to be applied to the circulatory system without reservations, since a state of dynamic equilibrium never exists more than momentarily (Wiggers).

When estimating the velocity and circulation time, it must also be kept in mind that the blood is composed of a liquid part, the plasma, and the corpuscular elements, the red and white corpuscles and the blood platelets.

For estimating the velocity in the arteries, many methods have been used, and by these the mean velocity has been calculated in the carotid artery and the aorta of various experimental animals. The velocity has been found to vary between 10 and 75 cm. per second. According to Tigerstedt, all these methods are not suitable for following, satisfactorily, the variations of the blood current.

Numerous studies have been made to determine how long a period is required for the blood to make a complete circuit. The concept of circulation time is a figment of the imagination. The term has been used, however, to denote the time required for a substance injected into the heart, or in man into a brachial vein, to reach some artery or branch where it can be detected. Various substances have been thus injected: decholine, histamine, saccharin, fluorescein, radium emanation, etc., and appropriate means for their detection have been devised. The "circulation time" has been found to vary between ten and twenty-six seconds, with an average of eighteen seconds.

Earlier investigations have established that the heart during its action performs an exceedingly complicated movement. By observing the position and form of the heart in the cadaver, with or without rigor mortis, and also from observations made with Ludwig, during physiological investigations on animals, Henke found the position of the atrio-ventricular ostia to be different during systole and diastole. Thus, the base of the heart seems to be nearer the apex during systole and farther away during diastole. Henke assumed, therefore, that the cardiac base makes a downward movement toward the apex during systole, and a regressive movement during diastole. That such a movement does occur during systole, with a return to the original position during diastole, has been shown by Filehne and Penzoldt, in experiments on rabbits and dogs. According to these authors, the ventricular base in this way comes to act as a pump piston in expulsion of the blood from the heart. It is pointed out by Rollet that, in a dissected heart from a frog (as well as from other vertebrate animals), the atrio-ventricular junction can be seen to approach the apex of the heart during systole and to move away from it

[1] The Second Annual Leo G. Rigler Lecture in Radiology delivered at the University of Minnesota, Nov. 26, 1946. A more complete and more fully illustrated paper on this subject will appear shortly in a book, "Roentgen Studies of the Lungs and Heart," to be published by the University of Minnesota Press.

during diastole. This up-and-down movement of the atrio-ventricular junction is the most definite movement observable in the heart.

These earlier physiological attempts at recording the cardiac movements were carried out with the thorax open and also, in many cases, with an open pericardium. Altered external pressure conditions are thus obtained, which may influence the movements of the heart. Such experimental results are not, therefore, a true expression of the cardiac movements under normal conditions.

In the radiological literature, Laurell was the first to point out the importance of the movements of the atrio-ventricular junction for driving out the blood from the ventricle. In a fundamental work on the radiology of the heart, he stated that the emptying of the ventricles does not occur by displacement of the apex and the lateral contours of the ventricles toward the center of the heart, as was earlier assumed by radiologists, but, above all, through displacement of the atrio-ventricular junction downward toward the apex.

While observing a few cases with calcification of the annulus fibrosus, Böhme was able to show, with the aid of fluoroscopy and kymography, that the atrio-ventricular junction performs a movement of about 2 to 3 cm. toward the cardiac apex during systole, and a slower retrograde movement during diastole. Sundberg has made a similar observation in a case of calcification of the annulus fibrosus. He was able to record by kymography a piston-like movement of this calcification toward the apex. He also estimated the quantity of blood that would be driven out by virtue of the movements of the atrio-ventricular junction, and found this to amount to 85 per cent of the total mass of blood expelled during systole.

In a recently published work, I explained how roentgencinematographic and electrocardiographic examinations had been simultaneously carried out on the hearts of sheep, with metallic indicators implanted in the myocardium in different parts of the left ventricular wall. One indicator was placed close to the atrio-ventricular junction, and the others within the peripheral parts of the ventricular wall. I was then able to show that the indicator placed at the atrio-ventricular junction made a sudden downward movement toward the apex. This movement began during, or immediately after, the QRS-complex. About half way between S and T the indicator made a rapid return to the original position, which was reached at the beginning of T. After T, or during diastole, this indicator remained fairly still again, to resume its rhythmic movements after the next QRS-complex. From these experiments it would appear that both the downward phase and the returning phase of the piston-like movement of the atrio-ventricular junction take place during systole, while this junction remains relatively quiet during diastole. It is clear, therefore, that the expulsion of the blood from the ventricle also requires a general contraction of the entire ventricular wall. No movement indicative of contraction was observed in the outer contours of the ventricular wall toward the center of the heart. The movements that can be observed in the outer contours of the ventricle consist in an oscillating and rotating movement of the heart as a whole.

Our knowledge of the dynamics of the heart is based mainly upon pressure curves taken simultaneously from different parts of the organ, and from the vessels. According to Lewis, the intraventricular pressure curve immediately before systole, and before the QRS-complex, shows a mild increase of pressure, which would be explained by contraction of the auricle (Fig. 1). In connection with the QRS-complex we get a rapid and considerable increase of ventricular pressure, beginning as the atrio-ventricular valves close and coinciding with the beginning of the first cardiac sound. The systole of the ventricle begins here. Immediately after this rapid and considerable rise in ventricular pressure, there is a rapid and parallel rise of the aortic pressure. According to Lewis, this rise of the aortic pressure would cor-

respond to the opening of the semilunar valves, indicated in the figure by the line S.O. The interval between closure of the atrio-ventricular valves and the opening of the semilunar valves is given by Lewis as approximately 0.05 second. This period corresponds to the time during which the ventricular pressure is on the increase but does not rise beyond the aortic pressure. No blood is leaving the ventricle during this phase. The ventricular and aortic pressures are then of equal magnitude, the curves being congruent and accompanying each other in the gentle rise following upon the rapid rise of pressure. The blood continues to leave the ventricle during this period. Suddenly the ventricular pressure is seen to drop rapidly in the neighborhood of the line indicated in the figure by S.C. The ventricular pressure here seems to drop below that of the aorta; this coincides with closure of the semilunar valves and diastole of the ventricle begins. The pressure curve falls rapidly, corresponding, according to Lewis, to the time of relaxation of the ventricular wall. A point is reached, denoted by A.V.O., which, Lewis states, corresponds to the opening of the atrio-ventricular valves. This would take place just after the end of T. The period between the closure of the semilunar and opening of the atrio-ventricular valves in man is approximately 0.05 second. The ventricular pressure continues to fall a little after the opening of the atrio-ventricular valves, but soon rises again while the ventricle fills with blood from the auricle. Lewis believes that the ventricle fills more rapidly during the earlier phase of diastole, less rapidly during its later phase.

Immediately after closure of the semilunar valves, we find on the pressure curve of the aorta a rise of brief and transient nature not to be found in the pressure curve of the ventricle. Lewis offers no explanation for this rise. The aortic pressure then drops slowly but not to the same degree as the ventricular pressure.

The pressure curve in the carotid artery shows a rise which comes 0.03 second later than the first rise of pressure in the aorta. This belated rise depends upon the time required for the transmission of the pres-

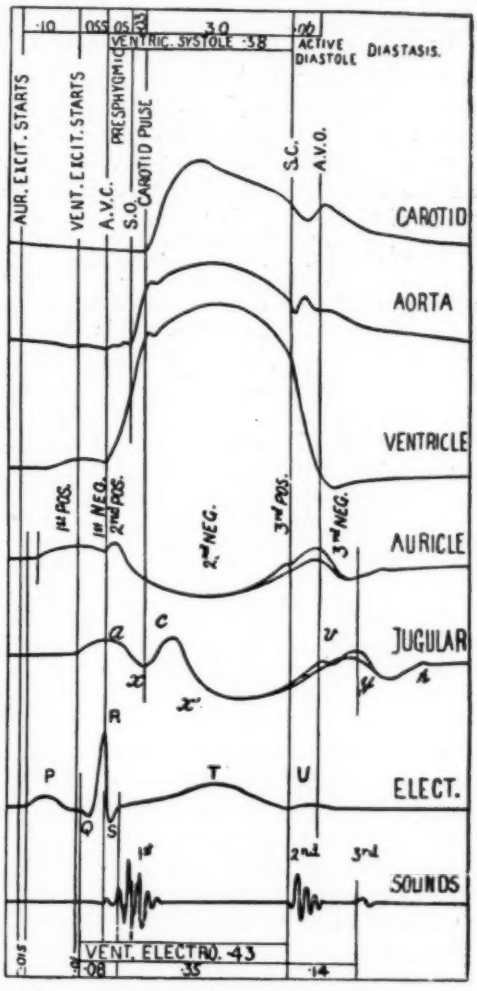

Fig. 1. Diagram (after Lewis) representing the curves of pressure in the carotid, aorta, left ventricle, and right auricle of the human subject, showing the supposed or ascertained time relations of these curves, the jugular pulse curve, the electrocardiogram, and apical heart sounds to each other. The diagram was constructed by Lewis, so far as possible from curves taken from man; but when such were non-existent, the diagram was completed by curves obtained from the dog. The times at which the excitation wave begins in auricle and ventricle are represented by vertical lines; the movements of the valves are similarly indicated. The scale of abscissa is 1 mm. = 0.015 second. A.V.C. and A.V.O. represent the closure and opening of the auriculo-ventricular valve, respectively; S.O. and S.C. represent the opening and closure of the semilunar valves, respectively. Other verticals are drawn at convenient points and the chief time intervals are marked above and below in seconds.

sure. The pressure curve of the carotid artery also shows a second rise of brief duration, similar to the second rise of pressure in the aorta.

The pressure curve of the auricle shows three elevations and three drops in the course of a cardiac phase. The first rise corresponds in time to the contraction of the auricle and is generally considered to be due to this contraction, since it disappears if the auricle is put out of action through tetanization and remains if the ventricular action is eliminated. The second rise in pressure coincides with the onset of ventricular systole. This rise is a result of the systole of the ventricle, and disappears upon elimination of the ventricular contraction. The third rise begins when the ventricular pressure has reached its maximum and is beginning to fall. Lewis considers this a stasis wave, caused by the collection of blood in the auricle during ventricular systole.

The first two falls in auricular pressure are attributed to three factors: relaxation of the auricle wall, creation of negative pressure in the chest following upon the ventricular systole, and a dragging upon the atrio-ventricular junction from the ventricle when systole begins. The third fall of pressure in the auricle occurs during ventricular diastole and is caused, according to Lewis, by the opening of the atrio-ventricular valves and by the blood flowing from auricle to ventricle.

Sjöstrand, Kjellberg, and Benner, by measuring the resistance for high-frequency currents in the heart, have shown that the A-V valves close and open in accordance with the above mentioned observations.

Böhme made attempts at taking cinematographic films of the fluoroscopic image after filling the heart and large vessels with thorotrast. He was able to obtain films at a rate of 20 per second, but he thought this rate too slow for observing and recording the circulation through the heart. He gives a careful description of the findings on fluoroscopy after this contrast filling of heart and big vessels and has published some roentgenograms and drawings of his investigations. He has, however, failed to analyze more closely the moving pictures, nor has he published any of them.

In his experiments Böhme found that the atrio-ventricular junction made a downward piston-like movement toward the cardiac apex. The central portion of this junction was then found to make greater movements than the lateral outline, causing it to bulge into the ventricle as a cone. Böhme considered that he had shown that the atrio-ventricular junction makes a downward movement during systole and a receding movement during diastole.

EXPERIMENTAL STUDIES: TECHNIC

For closer study of the circulation through the heart and the large vessels, and of the pumping mechanism of the heart, thorotrast has been injected into the jugular vein in rabbits, and the circulation has been recorded by cinematography of the fluorescent image produced by exposure to x-rays. An electrocardiogram has been taken simultaneously with the x-ray cinematography.

In the production of the fluorescent image, the x-ray tube has been regulated by means of the film camera. This has been done by means of a grid valve, so that the current to the x-ray tube has been momentarily activated each time the film in the camera has been still for exposure, and cut off when the film has moved. Thus the screen has emitted light only for that period in which a square of film has been exposed. A photo-cell has been fixed to the screen so that it registers on the electrocardiograph (film) every time the ciné-film is exposed. In consequence, the electrocardiogram has not only recorded the electrocardiographic curve, but also, synchronously, an indented curve, where each apex denotes an exposure. It is thus possible to determine from the electrocardiogram when the series of separate squares of film was exposed.

The x-rays which produce illumination of the fluorescent screen have been gen-

erated by a condenser apparatus giving a continuous direct current which makes the exposure of the ciné-film uniform. The use of a continuous direct current is also necessary for the recording of the exposures.

By measurements with various loads on the tube, we have been able to establish that the illuminating power of the screen increases in proportion to the increased tube tension and to the increased power of the current; whereas the illuminating power, as expected, decreases by the square of the distance between the x-ray tube and the fluorescent screen. We have found that the most suitable load on the x-ray tube in these experiments is a tube tension of 90 kv. and a current of 125 ma. In most experiments the distance between the screen and the x-ray tube has been one meter. With this load and with this focal distance, we have been able to carry out the filming at the rate of 64 pictures per second. The total time of exposure in the various experiments has varied between seven and ten seconds.

We have employed an ordinary film camera with a very sensitive lens (Biotar F 0.85:50 mm.), using Ciné Kodak Super XX film. The fluorescent screen is of a special design, emitting the kind of light to which the film is sensitive.

For these experiments on animals we have used thorotrast, which produces a very good contrast. Being a colloid, it mixes rapidly with blood without altering the osmotic pressure conditions. In experiments *in vitro* I have observed this rapid mixing with the blood, and on x-ray examination the contrasting blood gives a homogeneous shadow (Fig. 2, A). If this blood is allowed to settle after the addition of citrate, we observe, after a few hours, that the thorotrast adheres both to the white blood corpuscles floating uppermost and to the red corpuscles settling towards the bottom, as well as to the plasma, which forms the middle stratum. The white and red corpuscles, however, are richer in contrast matter than is the plasma (Fig. 2, B). Since the thorotrast mixes

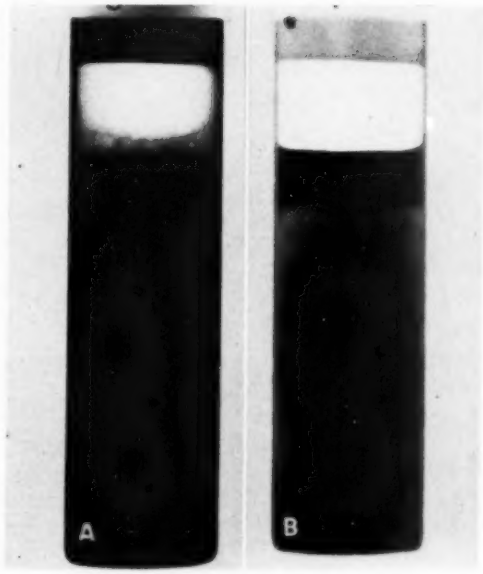

Fig. 2. A. Roentgenogram, *in vitro*, of the mixture of thorotrast and blood in the circulation as used in the experiments. This film was made immediately after the thorotrast had been injected into the blood. The contrast-filled blood shows a homogeneous shadow. B. Roentgenogram, *in vitro*, five hours after the injection, when sedimentation of the blood corpuscles has occurred. The thorotrast is seen to be mixed both with the red and white corpuscles as well as with the plasma.

so rapidly and well with the various components of the blood, gives a homogeneous shadow, and has, also, the same viscosity as the blood, it is an excellent contrast medium for these experiments and will produce a picture of the circulation in close agreement with the actual conditions.

The amount of thorotrast injected has been 20 gm., corresponding to 1–1.4 per cent of the body weight of the experimental animal. The blood thus becomes very rich in contrast matter even during the first phase of circulation. In later phases the blood and thorotrast are homogeneously mixed.

I have made in all 50 experiments on animals, with numerous filmings during both the first and subsequent phases of the circulation.

RESULTS

Viewing the films from the various experiments, one can observe clearly when

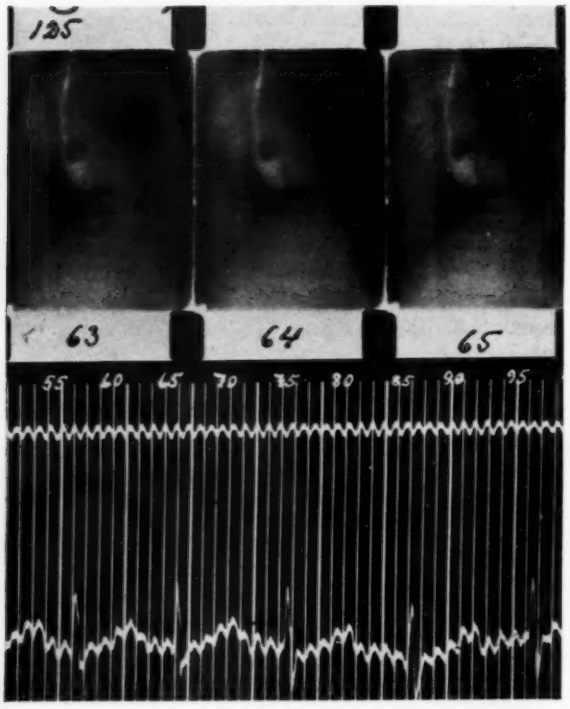

Fig. 3. Rabbit 125. Film squares 63 to 65 and the corresponding electrocardiogram with markings from the photo-cell shown as a wavy line above. Squares 63 and 64 show the filling of the right auricle and square 65 shows the first inflow through the ventricle corresponding to the time between P and Q.

the contrast blood first flows into the right auricle from the vena cava, then into the right ventricle, and out into the pulmonary artery. We can also discern easily when the blood, having passed the pulmonary circulation, flows into the left auricle, then into the left ventricle, and out into the aorta. During later phases we can see when the blood returns to the right auricle after completing the circulation.

During the circulation through the heart it is possible to observe distinctly that the auricles never empty completely into the ventricles, but retain great quantities of the contrast blood. The ventricles, however, appear to be completely exhausted, or very nearly so, at the end of systole.

The film also gives a clear picture of the rhythmic pumping mechanism of the heart. Here the dominating feature is the rapid piston-like displacement of the atrio-ventricular junction toward the apex, and its reverse movement, equally rapid. Then there is a short interval before the atrio-ventricular junction is again displaced toward the apex.

Details of the circulation through the heart and into the large arteries, and of the pumping mechanism of the heart, are not distinguishable when the film is viewed. On the other hand, if we scrutinize square after square of the film, comparing each with the electrocardiogram which is taken simultaneously, and in which the taking of the particular square is recorded, we can make a close study of the course of the circulation and determine at which stage in the cycle the various phases of the heart's action occur. The illustrations accompanying this paper represent individual squares of the motion picture film to-

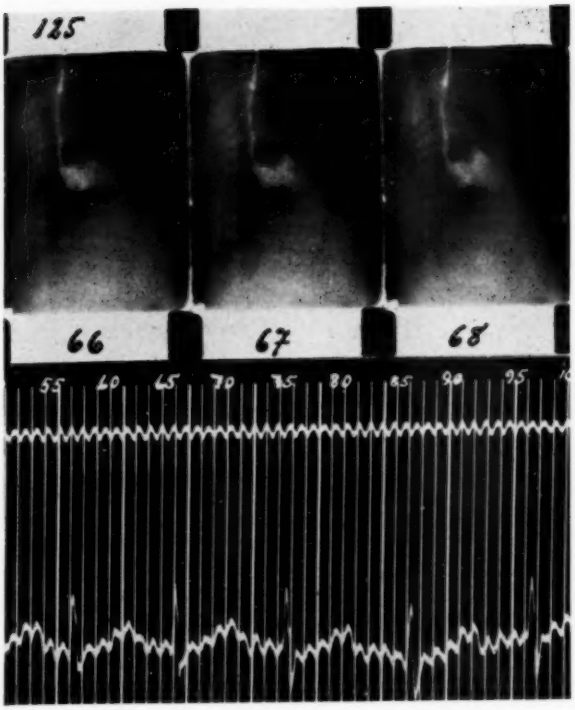

Fig. 4. Rabbit 125. Film squares 66 to 68 and corresponding electrocardiogram. The ventricle is filled, in square 66, at the onset of the QRS-complex, and the atrio-ventricular border is drawn to the apex. A large amount of contrast blood remains in the auricle. Square 67 shows the movement of the atrio-ventricular border toward the apex. The contrast blood has moved up to the arterial ostia. Square 68 shows that the atrio-ventricular border has made a retrograde movement back to its origin. The contrast blood is furthermore moved to the arterial ostia, yet there is no outflow from the pulmonary artery.

gether with the electrocardiographic and time tracings.

An approximate determination of the pulmonary circulation time may be made by establishing when the contrast blood first passes the pulmonary ostium into the pulmonary artery, and when it passes through the aortic ostium into the aorta. Even if the latter point in time can be determined only when the blood in the left half of the heart has attained such a concentration of contrast medium that it is distinguishable, the determination provides a relative measure of the circulation time which will be very near the true one, owing to the strong concentration of contrast matter. In these experiments the pulmonary circulation time has varied between 1.2 and 2.5 seconds, with a mean value of 1.5 seconds. In previous investigations the mean time of the entire circulation has been established at approximately 18 seconds, so we find that the time for the pulmonary circulation is about one-twelfth of the total. This agrees with the fact that the quantity of blood contained in the lungs is one-twelfth of the total amount of blood.

When the contrast blood is for the first time pressed out from the ventricles into the pulmonary artery and the aorta—which occurs with great velocity—the head, or leading portion of the comparatively narrow jet of contrast matter be-

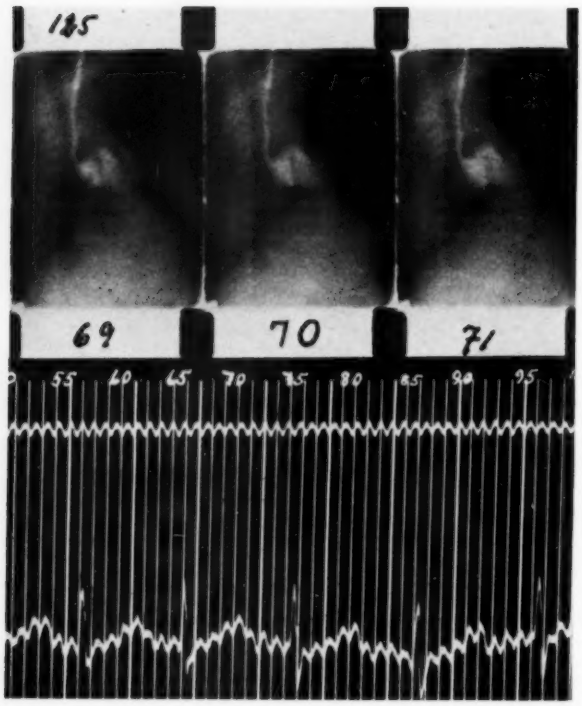

Fig. 5. Rabbit 125. Squares 69 to 71. The first outflow of the pulmonary artery is here visible. Square 69 corresponds to the beginning of T.

comes more and more mixed with blood. The head of the jet thus becomes thinner, and cannot be clearly distinguished in the pictures. Its appearance and exact position cannot therefore be determined with this method. Neither can the systolic velocity of the blood stream be definitely established. It is, however, possible to determine approximately when the blood has become filled with some contrast matter in a given portion of the vessels, so that an approximate minimum value of the systolic velocity may be obtained. In the various experiments, such a minimum value has been measured at 300–650 cm. per second in the aorta and 120–200 cm. per second in the pulmonary artery. These minimum figures are considerably higher than those previously assumed. Broemser, for instance, has calculated the systolic velocity in the aorta at 160 cm. per second.

Judging from these observations, the velocity in the aorta would be greater than that in the pulmonary artery. According to Quain, the aortic ostium is narrower than the pulmonary ostium. To permit the same amount of blood to pass the two ostia in a given time, the velocity in the aorta must be greater than that in the pulmonary artery.

The circulation through the heart, and the pumping mechanism of the heart, can be closely followed by a study of the separate exposures. As these have been taken at intervals of 1/64 second and the electrocardiogram shows exactly when they have been exposed, these film squares enable the worker to study the details of the circulatory cycle.

The films display distinctly how the auricles are being filled continuously, possibly with a slight increase immediately after the QRS-complex (Fig. 3). During presystole between P and Q one clearly

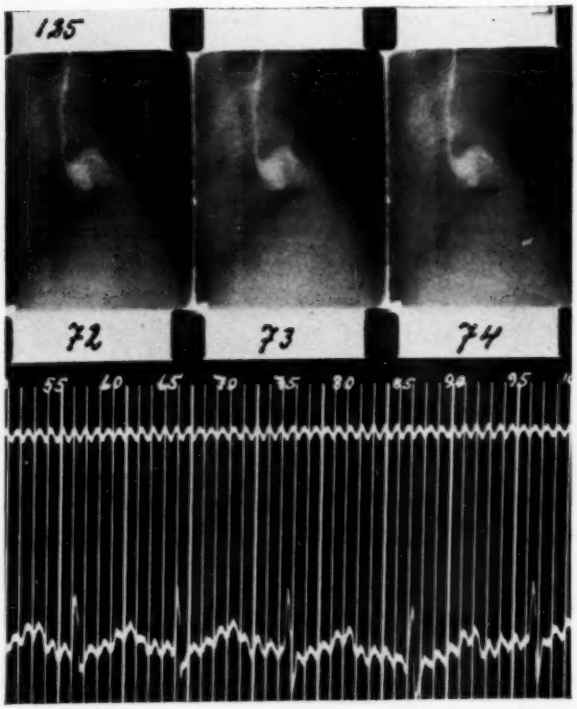

Fig. 6. Rabbit 125. Squares 72 to 74. Square 72 corresponds to the end of T and shows the end of the outflow from the ventricle. The semilunar valve is closed and the ventricle is empty. There is a large amount of blood in the auricle. No visible filling of the ventricle is seen in squares 73 and 74.

sees the rapid emptying of the auricles and the filling of the ventricles with contrast material. On the other hand, it is not possible to distinguish any definite collection of contrast blood in the ventricles during diastole, though the possibility is not excluded that an insignificant quantity of blood, not visible to the eye, may flow into the ventricles during this phase. The experiments appear to demonstrate, therefore, that the rapid stream of blood to the ventricles occurs during presystole.

The inflowing contrast blood appears to flow toward the ventricular wall just above the apex, and then to be distributed along the ventricular walls; a few return currents are distinguishable in the periphery toward the atrio-ventricular junction. At the commencement of the QRS-complex the inflow of contrast blood to the ventricles ceases, and the valves close. Great quantities of the blood then remain in the auricle (Fig. 4). Immediately after this, the atrio-ventricular junction is seen to move suddenly toward the cardiac apex. The central part is observed to move farther down than the peripheral parts, so that the atrio-ventricular junction bulges into the ventricle like a cone. The amplitude of this downward movement is approximately 0.5 cm. The downward movement changes rapidly into a retrograde one about halfway between S and T, and reaches the initial position at the beginning of T (Fig. 5). Then the atrio-ventricular junction stands still until the next QRS-complex, when the movement is rhythmically repeated.

The downward movement of the atrio-ventricular junction causes the volume of the ventricle to decrease by what may be estimated as 0.5 to 1.0 c.c. in the various animals. This estimate is based on the

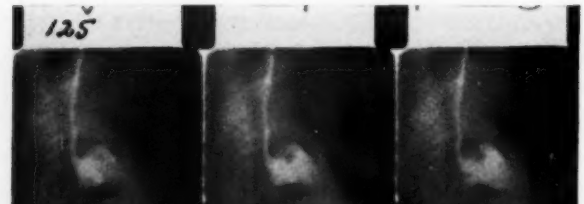

Fig. 7. Rabbit 125. Squares 75 to 77. Inflow to the ventricle has started in square 75, which is somewhat later than T. The inflow to the ventricle has continued between 75 and 76. Square 76 corresponds to Q and the atrio-ventricular border has started its movement to the apex. A large amount of contrast blood remains in the auricle. Square 77 shows a further movement of the atrio-ventricular border to the apex and contrast blood in the ventricle moves up to the arterial ostia.

assumption that the atrio-ventricular junction is circular and that the whole surface is pressed into the ventricle uniformly.

At the same time that the atrio-ventricular junction commences its retrograde movement, the inner contour of the cardiac apex, together with the contrast relief, is seen to be displaced upward, while the outer contour does not alter its position. The displacement of the inner contour would thus depend on a swelling of the ventricular wall caused by the contraction of the ventricle. The contrast blood in the ventricles is simultaneously displaced toward the arterial ostia. Immediately before T, the contrast blood is observed to pass through the arterial ostia into the pulmonary artery and the aorta. This expulsion continues during T, and ceases abruptly at the end of T, when the ventricles are exhausted of almost all the contrast medium (Fig. 6). The empty ventricles are then distinctly outlined against the contrast-containing auricles, the pulmonary artery, and the aorta. The closing of the semilunar valves would thus seem to occur in accordance with previous investigations. The ventricles are observed to be empty of contrast matter between T and P, after which they are seen to fill rapidly with contrast blood again (Fig. 7).

Judging from the observations made in these experiments, the rapid inflow of blood to the ventricles takes place during presystole, and not, as generally held, at the beginning of diastole. During the latter period no definite collection of contrast

blood may be noticed in the ventricles, although it is not entirely out of the question that a slight filling takes place. The expulsion of contrast blood from the ventricles would also seem to occur later than demonstrated by pressure determinations. According to these experiments, the expulsion through the arterial ostia occurs at the beginning of T, and not immediately after S, as shown by pressure determinations. The closing of both the atrio-ventricular valves and the semilunar valves appears to take place in accordance with previous experience. However, these experiments have been carried out under physiological conditions which have differed from those during the determinations of pressure, so that no direct comparison can be made.

How can one interpret the course of the systolic contraction? It seems probable that the systolic contraction of the ventricle begins with a contraction of the interventricular septum, in which the septum is shortened and the central part of the atrio-ventricular junction drawn toward the cardiac apex. In connection with the contraction of the septum, and the movement of the atrio-ventricular junction toward the apex, the papillary muscles emanating from the septum will contract and prevent the atrio-ventricular valves from being forced into the auricles. The contraction will then proceed continuously along the septum to the cardiac apex. When this contracts, the wall swells and the inner contour of the apex moves, together with the septum, toward the base, the retrograde movement of the atrio-ventricular junction taking place simultaneously. Then the contraction will continue along the external ventricular walls up toward the arterial ostia. The lumen of the ventricles is compressed at the same time, since the inner contour approaches the atrio-ventricular junction and the arterial ostia.

This continuous systolic contraction from the septum to the cardiac apex, and further along the external ventricular walls to the arterial ostia, starts in connection with the commencement of the QRS-complex and finishes at the end of T, when the contrast blood has been almost completely expelled from the ventricles and the semilunar valves are closed. The ventricular walls will then lie close to each

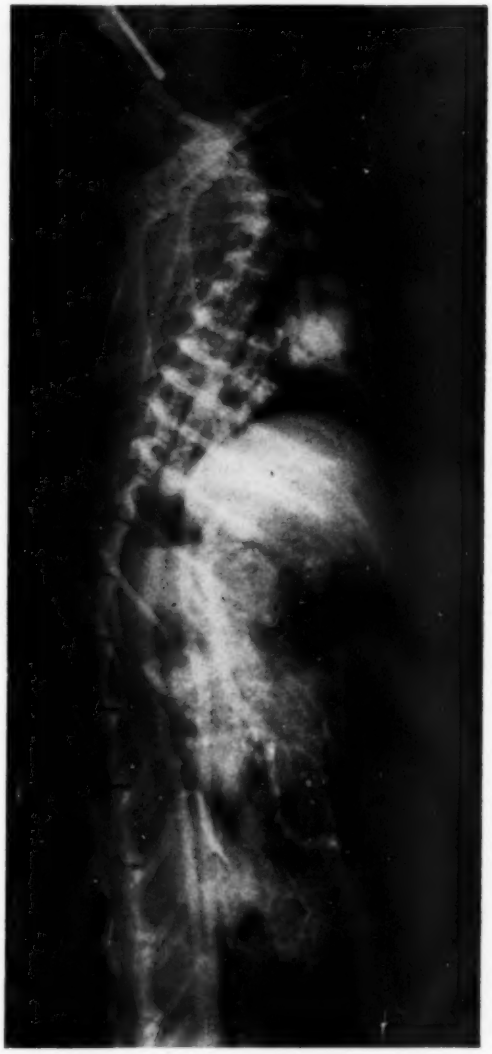

Fig. 8. Rabbit 106. Roentgenogram of the entire rabbit, lateral view, taken between T and P. The auricles are filled with contrast blood, while the ventricles are empty. Through the ventricles the contrast-filled coronary arteries are visible. The atrio-ventricular junction is clearly in evidence. The whole aorta, the pulmonary artery and the venae cavae are also seen.

other, leaving only a fissure-shaped ventricular lumen.

A roentgenogram in the lateral view of the whole animal, made after thorotrast injection, is reproduced in Figure 8. This indicates in more detail the appearance of the contrast medium in the heart and large vessels.

This interpretation of the course of the systolic contraction explains the observations made in these experiments and is in accord with the analysis made by Lewis in regard to the extension and time of the irritation of the ventricular surface.

Systole once complete, the ventricles will not relax immediately; which might explain the fact that no filling of the ventricles is distinguishable until P, when the rapid flow of contrast blood to the ventricle sets in.

SUMMARY

The study of cardiac contraction and its relationship to the circulation by means of indirect roentgencinematography of the contrast-filled circulatory system is described. The timing of the various phases of the circulatory cycle was determined by means of electrocardiograms simultaneously made. From the observations made in this way, certain interpretations of the physiology of the circulation have been derived.

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SUMARIO

Estudios de la Circulación con la Roentgenocinematografía

Una técnica elaborada permite estudiar la contracción cardíaca y su relación con la circulación por medio de la roentgenocinematografía del aparato circulatorio. Como medio de contraste se utilizó el torotrasto, por mezclarse bien con la sangre y producir un cuadro de la circulación que concuerda intimamente con la realidad. Los electrocardiogramas se obtienen simultáneamente y se registran de modo que es posible determinar por ellos en qué fase del ciclo circulatorio se expusieron los distintos cuadrados de película. Con esa técnica, se hicieron observaciones en 50 conejos.

A juzgar por esas observaciones, la rápida entrada de sangre en los ventrículos tiene lugar durante la presístole, y no, como se sostiene generalmente, al principio de la diástole. La expulsión de la sangre de los ventrículos tiene también lugar aparentemente más tarde que lo que indican las determinaciones de la presión.

De acuerdo con estos experimentos, la expulsión de la sangre por los orificios arteriales ocurre al comienzo de T y no inmediatamente después de S, según han demostrado los estudios de la tensión. El cierre de las válvulas auriculoventriculares y semilunares parece tener lugar de conformidad con las observaciones anteriores.

Parece probable que la contracción sistólica del ventrículo comience con una contracción del tabique interventricular y sea continua del tabique a la punta del corazón, y más allá, a lo largo de las paredes exteriores de los ventrículos hasta las bocas de las arterias, principiando con el comienzo del complejo QRS y acabando al final de T, cuando la sangre ha sido ya casi completamente expulsada de los ventrículos y las válvulas semilunares están cerradas. Las paredes ventriculares quedarán entonces muy próximas entre si, dejando únicamente una especia de grieta ventricular. Ya terminada la sístole, los ventrículos no se dilatan en el acto, lo cual puede explicar por qué no se observa repleción de los mismos hasta P, cuando comienza la rápida penetración de sangre en los ventrículos.

Preliminary Observations on the Effects of Irradiation upon the Chylomicrons in Human Blood[1]

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THE RADIOLOGICAL literature of recent years has deepened our knowledge especially as regards the biological effect, both local and general, of roentgen and radium rays. While earlier the response of the skin was the chief concern of the radiologist, more recently the response of the bodily organs has attracted increasing interest. The general effect—or effects—of irradiation are unfortunately but partially known, and it is as yet impossible to estimate fully their importance more than the mechanism of origin. It seems probable, however, that local and general irradiation effects are in intimate relation to each other.

Long ago it was noted that the massive application of roentgen rays over the abdominal region produced grave symptoms. This state is known as "radiation sickness," and its symptoms resemble those of shock arising from other causes. Other features, such as low metabolism, increased blood sugar and non-protein nitrogen hypochlorhydria, and decreased alkaline reserve, are also like those of shock. For that reason the conclusion has gradually been reached that, as an effect of irradiation, there arise in the damaged and dying tissues substances which have a toxic effect on the organism when resorbed. When investigating this circumstance experimentally, Zacherl observed that if one of two parabiotically united albino rats received an injurious dose of rays the other also suffered. Gradually it was observed that irradiation on one hand and histamine-like substances on the other produce in the organism phenomena which not only greatly resemble each other, but resemble also shock arising from other causes. The histamine (H-substances) theory has proved valuable for the understanding of many of the effects of irradiation.

As is apparent from the literature, in various animal species the lethal dose of roentgen rays, when given to the whole body in one session, produces definite injury to liver cells, as indicated by increasing amounts of sudanophil fat. Likewise it has been stated that chronic administration of histamine produces in dogs the same histologic picture as irradiation, including extensive accumulation of sudanophil fat around the central vessels of the liver lobules.

The accumulation of sudanophil fat around the central vessels of the liver lobules reported in irradiated animals, together with the fact that this phenomenon can hardly be considered as a simple direct radiation effect, has led the author to study the fluctuations of the so-called "mobile visible lipids" in the blood stream during irradiation. There is hardly any mention to be found in the literature of the behavior of lipids in the blood between the administration of a fatty meal and their deposition in the tissues, when the subject is receiving roentgen or radium irradiation. Nor is there any direct mention of the effects of histamine administration on fat metabolism. It has been the purpose of the author, therefore, to determine (1) whether there can be established changes in the amount of mobile visible lipids in the blood stream as a result of irradiation, and (2) whether the changes in lipid metabolism, if such changes occur, may perhaps be of the same type as those produced by histamine administration.

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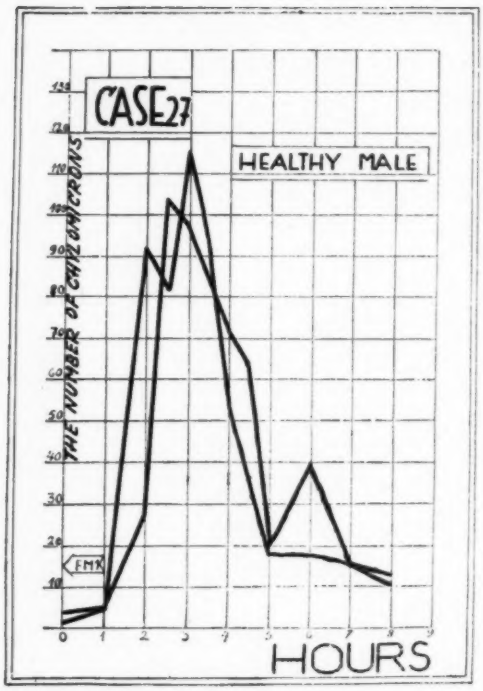

Fig. 1. Case 27, healthy male, aged 25. Both curves constructed during postprandial lipemia after a single fatty meal. The curves (calculated on different days) show how, in the same individual, under the same external conditions, the absorption rhythm of mobile visible blood lipids remains constant.

MATERIALS AND METHODS

An essential requirement for the solving of these questions was a suitable method of investigation. The solution was found in the idea of the "chylomicron," first used by Gage and Fish (1924). This name is given to tiny droplets of fat visible in the blood plasma, after a fatty meal, in light reflected from their surface, under the dark-field microscope. The designation is appropriate, *chylos* signifying that the particles enter the blood stream from the area of intestinal absorption, and *micron* indicating their small size. By counting the number of chylomicrons at stated intervals following a certain method, after a fatty meal, a so-called "chylomicron curve" can be constructed.

Our studies have been made exclusively on human beings, the entire material consisting of 32 individuals (10 males and 22 females). The persons under investigation were subject to the same external conditions throughout the course of the investigation. The irradiation was given in part in the form of deep roentgen therapy and in part as telecurietherapy. For the histamine studies 0.5 c.c. of histamine acid phosphate ("Endo," U.S.P.), which consists of about one-third histamine, by weight, was used. All the results were recorded as graphic curves, showing the chylomicron counts at half-hour intervals up to eight or ten hours. The method was the same as that of Gage and Fish.

For a study of this type, it is most important that the method used be as reliable as possible. Elimination of possible errors was therefore a matter of particular concern. With this in view, the following conditions were observed: the persons were kept under the same conditions during the whole observation period; the investigations were begun after a rest period of twelve hours; the examination of the blood was always performed by the same person with the same instruments.

PROCEDURE AND RESULTS

Though the chemical character of chylomicrons is not finally solved, there is substantial proof that at least the majority of them are in the form of lipids. The general opinion as to the chemical composition of these corpuscles is that they bear a certain relation to fatty food and that they consist of fat and/or lipoids. From the point of view of modern colloid chemistry, it seems probable that these oil drops are covered by a folded film of protective proteins, by the help of which they can form a thermodynamically stable emulsion. In this work the above conception of chylomicrons was accepted. The amount of chylomicrons was always found to be in direct proportion to the amount of fat ingested.

During the investigation it became apparent that the metabolic rhythm of the mobile visible blood lipids, *i.e.*, the chylomicron curve, was characteristic for each individual, and its form for the same indi-

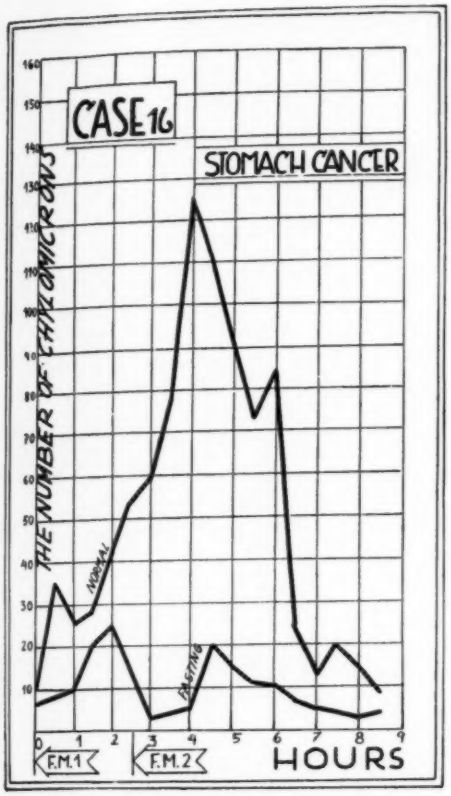

Fig. 2. Case 16, female, aged 35, operated upon for stomach cancer. The upper curve presents fluctuations in the chylomicron count during postprandial lipemia after two fatty meals (F. M. 1 and F. M. 2). The lower curve was constructed during a "fasting" period in the same case.

vidual in same external conditions remained comparatively constant (Fig. 1). There were, however, individuals whose chylomicron curve differed from the so-called "normal" curve. In some the chylomicrons in the blood increased very rapidly after the fatty meal, the maximum was very high, and the curve fell more abruptly. In others, though no second fatty meal was given, the curve displayed one or more "after peaks." In individuals with this type of curve the maximum value did not rise as high as in the former cases, but when in the two types the areas defined by the 0-plane and the curve were compared, they were found to be about equal. In other words, roughly calculated, the total

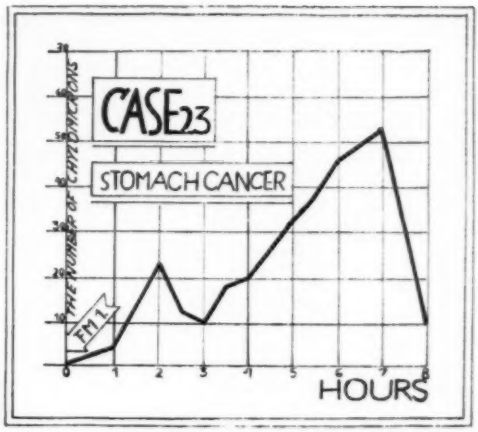

Fig. 3. Case 23, female, aged 53, operated upon for stomach cancer. The chylomicron curve during postprandial lipemia after a single fatty meal (F. M. 1), at the beginning of the observation period. No irradiation therapy.

amount of mobile visible blood lipids during postprandial lipemia was about the same in different individuals, provided they were healthy. In such persons the chylomicron curve usually reached its maximum three hours after the fatty meal and fell to the 0-plane again on an average of eight hours after the meal, practically irrespective of whether the person in question had had one or two fatty meals, provided the total amount of fat taken was the same. In persons with cancer of the stomach who had never been treated with irradiation, the chylomicron maximum was not reached until a little later (Figs. 2 and 3).

When irradiation was given to persons considered healthy, it had a definite reducing effect on the mobile blood lipids, especially when given comparatively soon after a fatty meal, and to certain regions of the body (Fig. 4). Irradiation of cancer-bearing patients produced similar changes in the amount and metabolic rhythm of blood lipids.

In conformity with the clinical observation that the site of irradiation has a great importance for the general condition of the patient, it was established in this work that changes in the metabolic rhythm of mobile visible blood lipids varied according to the body region irradiated. Irradiation

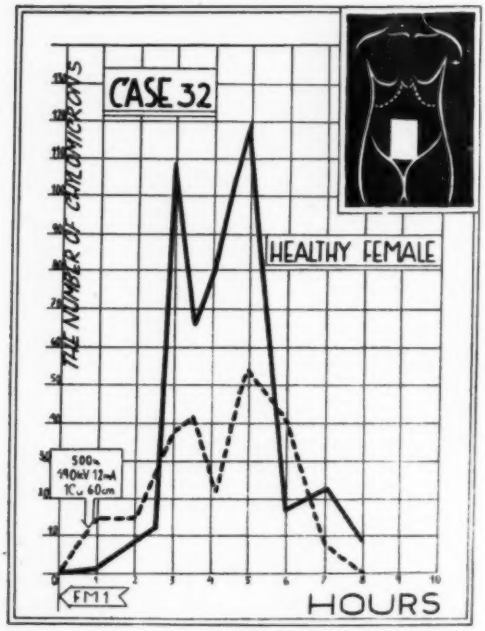

Fig. 4. Case 32, healthy female, aged 77. The upper curve presents fluctuations in the chylomicron amount during postprandial lipemia after a single fatty meal, without treatment. The lower curve (dash line) shows alterations in the resorption rhythm caused by roentgen irradiation 45 min. p.c. (irradiation field 10 × 15 cm.; intensity 30 r/min.).

to the organs in the lower abdomen (Fig. 5) or the pelvis, as also the area of the bifurcation of the common carotid artery (Fig. 6), caused distinctly greater changes, both in the amount and in the absorption rhythm of the blood lipids. Further, it appeared that, with irradiation directed to the liver, the changes were very severe (Fig. 7). It was demonstrated, also, that the interval between the taking of fatty food and subsequent irradiation was of great importance: the shorter the time that had elapsed, the greater the effect of irradiation seemed to be.

The observations indicated, at least partly, that in persons with a disposition to irradiation sickness, the treatment caused more marked alterations in the blood lipid occurrence (Figs. 6 and 7) than in others.

With the histamine theory, discussed earlier in this paper, in mind, histamine acid phosphate was injected intramuscularly in both healthy, non-tumor-bearing individuals and cancer patients. It was found that histamine administration, when performed at a suitable point of time, effected marked changes in the lipid metabolism in the blood in healthy persons (Fig. 8). The effect of the histamine be-

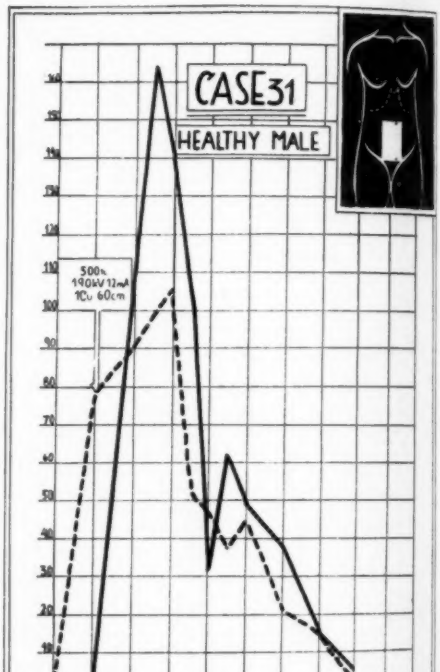

Fig. 5. Case 31, healthy male, aged 49. The lower curve (dash line) shows fluctuations of the chylomicron count after roentgen irradiation given one hour p.c. Irradiation factors as in Fig. 4.

gan about one hour after administration, and the maximum chylomicron count was only half as high as in untreated persons. In analogy with the effect of irradiation, in cancer-bearing patients the histamine had also a strongly reducing effect on the amount of blood lipid. The effect was usually the greater, the sooner after the fatty meal the drug was administered. In some cases, the histamine acid phosphate, when given before the meal, prevented

entirely the appearance of chylomicrons in the blood (Fig. 9).

DISCUSSION

One of the reasons why the changes in the blood lipid metabolism caused by irradiation have not attracted more attention has, without doubt, been the lack of a suitable and wholly reliable method of investigation. In earlier works of this character, various quantitative-chemical methods have been used to determine the lipid fractions of the blood. With such procedures the possibilities of error have been great. Neither have the relations of different individuals, on the one hand, to irradiation, and, on the other hand, to fat metabolism in general, been taken sufficiently into consideration.

In the work now reported, an attempt has been made to study the metabolism of the mobile visible blood lipids during irradiation, with as simple a method as possible. Control experiments have also been performed entitling us to draw certain conclusions: first, that in the same person the lipid metabolism is practically constant; second, that this regularity remains the same from a quantitative point of view, parallel experiments strengthening the basis of the investigation. Because of this, it is believed that the results obtained on the basis of the calculations of the chylomicrons at different intervals are very nearly correct, or at least proportional to one another.

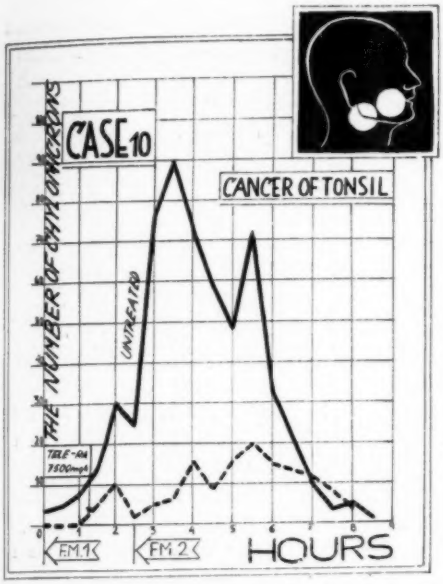

Fig. 6. Case 10, female, aged 64, with cancer of the tonsil with metastases in the neck. The lower curve represents changes in the chylomicron count following telecurie treatment (7,500 mg. hr.) immediately after the first fatty meal (F. M. 1). This patient had symptoms of radiation sickness.

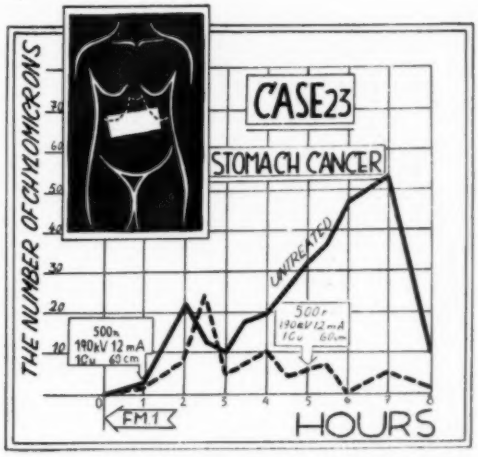

Fig. 7. Case 23, female, aged 53, operated upon for stomach cancer. The lower curve represents fluctuations in the chylomicron amount caused by two roentgen irradiations during the same day (during postprandial lipemia after a single fatty meal). This patient had symptoms of radiation sickness.

During the investigation it became apparent, *first*, that irradiation caused definite changes in the metabolism of mobile visible lipids in human blood; *second*, what is very important, that changes of an exactly similar kind may be brought about by histamine acid phosphate administration. Further it appeared that, when irradiation was given to different regions of the body, different changes in the metabolic rhythm appeared, according to the region irradiated. When the liver was irradiated, the changes were especially severe. What, then, is the cause of the fluctuation and/or decrease of chylomicrons in the blood stream? When the observations made are compared with those of other investigators, according to

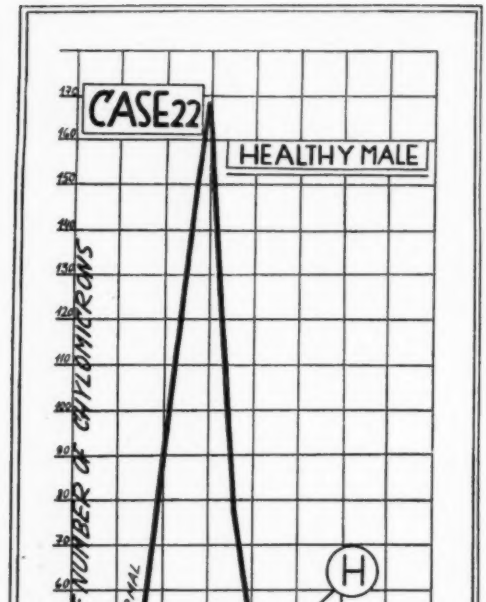

Fig. 8. Case 22, healthy male, aged 19. Both curves constructed during postprandial lipemia, after a single fatty meal at the beginning of the observation period. The upper curve represents the normal metabolic rhythm of visible blood lipids by this individual. The lower curve denotes fluctuations in this rhythm after injection of 0.5 c.c. of histamine acid phosphate.

which large accumulations of sudanophil fat around the central vessels of the liver lobules have been established as an effect of irradiation in experimental animals, these phenomena associate with one another to one purposeful event. Jenkinson and Brown, for instance, have illustrated the effect of roentgen rays on the capillary beds, with resultant anoxemia of cells, local capillary dilatation, and loss of plasma into the tissues. It is of importance that they also pointed out that irradiation sickness is most likely to follow irradiation of those regions of the body possessing the largest capillary beds and that, to combat it, they recommend administration of vasoconstrictors. It has been shown that especially deep roentgen irradiation of the abdomen causes the complete and characteristic syndrome of shock. This is accompanied by *hemoconcentration*, including diffuse congestion of the lungs, of mucous and serous surfaces, etc. Dale, Laidlaw, and Richards were led to conduct experiments with histamine because of the fact that it produces a shock-like failure of circulation when injected into the blood stream. The erythrocyte count, hematocrit concentration, and hemoglobin percentage indicated a marked concentration of the blood as shown by a loss of 50 to 60 per cent of the original plasma volume.

If, as seems really to be the case, irradiation and histamine administration lead to hemoconcentration when the permeability of the capillaries increases, we may consider the alterations in the amount of mobile visible blood lipids, especially their decrease, as partly attributable to the same cause. There is a measure of histologic evidence that chylomicrons may pass in streamlines through the cells, and histochemical methods have shown that during normal absorption, minute streams of fat can be demonstrated in the outer parts of the epithelial cells.

The studies recorded here have shown clearly that though there may be an increase in the chylomicron content of the blood after either irradiation or histamine administration when applied late, these procedures caused a sharp drop in the chylomicron curve, differing markedly from that in untreated controls. This to the author's mind is unconditional evidence that irradiation and histamine administration serve to intensify the disappearance of mobile visible blood lipids. In other words, *these particles escape more easily from the blood stream because of the increased permeability of the capillaries*.

Where do the mobile visible blood lipids go after disappearing from the blood

stream? When human material is concerned this problem cannot, of course, be finally solved. When, however, we consider the observations made by other authors, according to which chronic injection of histamine produces in dogs the same histologic picture as irradiation, including extensive accumulation of sudanophil fat around the central vessels of the liver lobules, we are able to arrive at an explanation.

SUMMARY

An attempt was made to determine the effects of roentgen or radium rays on the mobile visible lipids in human blood following administration of a fatty meal, before the lipids were deposited in the tissues. As a method of investigation, instead of quantitative chemical determinations, which are subject to considerable error, chylomicron counts were obtained at half-hour intervals. Observations were made on 32 individuals, and every precaution was taken to avoid the possibility of error.

It was found that irradiation regularly produced changes in the amount and metabolism of the visible blood lipids. Further it was found that, to produce changes, the irradiation must be done within a given time interval after the ingestion of the fatty food. It appeared, also, that irradiation of certain regions of the body, as the abdomen, the pelvis and the bifurcation of the common carotid was followed by a particularly marked effect.

With the histamine theory in mind, the effect of intramuscular injections of histamine acid phosphate was also investigated. Such injections, suitably timed in relation to the fatty meal, effected changes in the lipid metabolism comparable to those following irradiation.

In persons with symptoms of radiation sickness, the changes in the blood lipids were particularly severe.

It is assumed that the decrease and/or disappearance of the mobile visible lipids observed in these studies is an effect of hemoconcentration due to increased permeability of the capillaries caused by irradiation or histamine administration.

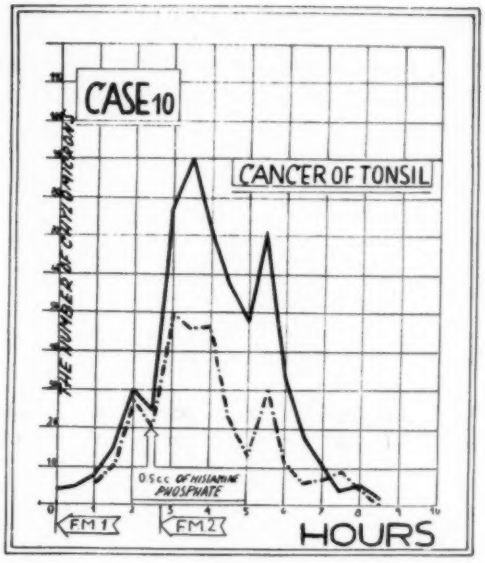

Fig. 9. Case 10, female, aged 64, with cancer of the tonsil (the same patient as in Fig. 6). The lower curve denotes fluctuations in the chylomicron count following intramuscular injection of 0.5 c.c. of histamine acid phosphate two and a half hours after the first fatty meal (F. M. 1).

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(For Spanish Summary, see following page)

SUMARIO

Observaciones Preliminares acerca de los Efectos de la Irradiación sobre las "Quilomicras" en la Sangre Humana

Tratóse de determinar el efecto de los rayos X o el radio sobre los "lípidos visibles movibles" que hay presentes en la circulación sanguínea del hombre después de la administración de una comida grasa, antes de fijarse en los tejidos. Tomáronse para observación 32 personas, comprendiendo sujetos normales y cancerosos de varios tipos. Como medida del efecto, se determinó el número de "quilomicras" en la sangre a plazos de media hora, usándose el término de "quilomicras" para designar las minúsculas gotillas de grasa visibles en el plasma sanguíneo, en la luz reflejada de su superficie, en el campo oscuro del microscopio (Gage y Fish). Hiciéronse observaciones semejantes después de administrar histamina, a fin de averiguar si las alteraciones producidas eran comparables a las derivadas de la irradiación.

Descubrióse que la irradiación ejercía un efecto reductor bien definido sobre la cantidad de lípidos visibles en la sangre, sobre todo cuando se hacía poco después de la comida de grasa. También pareció que la irradiación de ciertas zonas del cuerpo, notablemente el abdomen, la pelvis y la bifurcación de la común carótida, provocaba efectos más notables que cuando se aplicaba a otros sitios. Esto sucedió por igual en individuos sanos y cancerosos. Se notó también que la administración de histamina, en forma de inyecciones intramusculares del fosfato ácido, producía una notable disminución de la cantidad de lípidos sanguíneos. El efecto fué en particular notable en las personas que revelaban síntomas de enfermedad de radiación.

Recapitulando, se da por sentado que la disminución y/o desaparición de los lípidos visibles movibles de la sangre, observadas en estos estudios, procede de la hemoconcentración debida a la hiperpermeabilidad de los capilares provocada por la irradiación o la administración de histamina.

Effects of Small Daily Doses of Fast Neutrons on Mice[1]

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THE POTENTIAL danger of overexposure to radium rays and roentgen rays is generally recognized. Likewise, it is known that even low doses of these radiations will, if received at frequent intervals over a long period, eventually produce recognizable damage. The advent of the cyclotron and the nuclear reactor has presented another radiation to be dealt with, namely, the neutron. This radiation is biologically effective, and in some respects is much more dangerous than x-rays or radium. The maximum permissible daily exposure for radium and x-radiation is set at 0.1 r per eight-hour day for a five-and-a-half-day week (1). It is now necessary to establish a safe limit for daily exposures to neutron radiation. It has been the purpose of the present investigation to study the effects of small daily doses of fast neutron radiation to the whole body of laboratory mice.

MATERIALS AND METHODS

Animals: In the preliminary experiments, male and female mice of the Swiss strain (Rockland Farms) were used. In the main experiments, animals of the CF_1 strain (Carworth Farms) were also used. These animals were from four to six weeks of age at the beginning of the experiments. They were fed on Rockland mouse diet, with water available at all times. The sexes were kept separate. The animals were not crowded, and care was taken to keep the same original groups of males together, as the introduction of a new animal had been found to encourage fighting.

Examinations: Blood counts were taken twice a week (in the long-term experiments) on animals of each experimental and control group. Each individual was numbered and animals were taken serially for this examination. Since there were 25 animals in each group, there was a long lapse of time between counts on the same individual, except toward the end of the experiment. Small blood pipettes[2] were used (volume about one-quarter that used for human samples) and were found to be reliable. Blood counts consisted of a red cell count, white cell count, hemoglobin determination (photo-electric hemoglobinometer), and a differential blood count made from a smear.

The animals were examined closely every day for general condition, for signs of epilation, etc., visible or palpable tumors, infection, and eye defects. Each animal was weighed when its blood count was made, and once a week all were weighed. No animal was sacrificed until over half of the individuals in a particular group had died. Autopsies were done as soon after death as possible and, if tissues were fresh enough, they were preserved and prepared for microscopic examination. Tissues usually saved were bone marrow (sternum), spleen, gonad, lungs, kidney, adrenal, liver, and intestine. If a tumor or inflammatory condition was found in some other organ, it was, of course, added to the tissues to be studied microscopically.

Radiation: The neutron radiation employed was produced by the 36-inch cyclotron in the Pupin Laboratories of Columbia University. A broad beam of neutrons was used (180° from primary beam) and the irradiation box was 28 inches from the source. Exposures and calibrations were made in a large semicircular container of lead (Fig. 1). The beam was filtered by 3 inches of lead. The top, back, and sides of the chamber were of lead 1 inch in

[1] This document is based on work performed under Contracts W7405-eng-50 and W31-109-eng-14 for the Manhattan Project and the Atomic Energy Commission. Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

[2] Similar to ones designed for the Rochester University Radiation Laboratory.

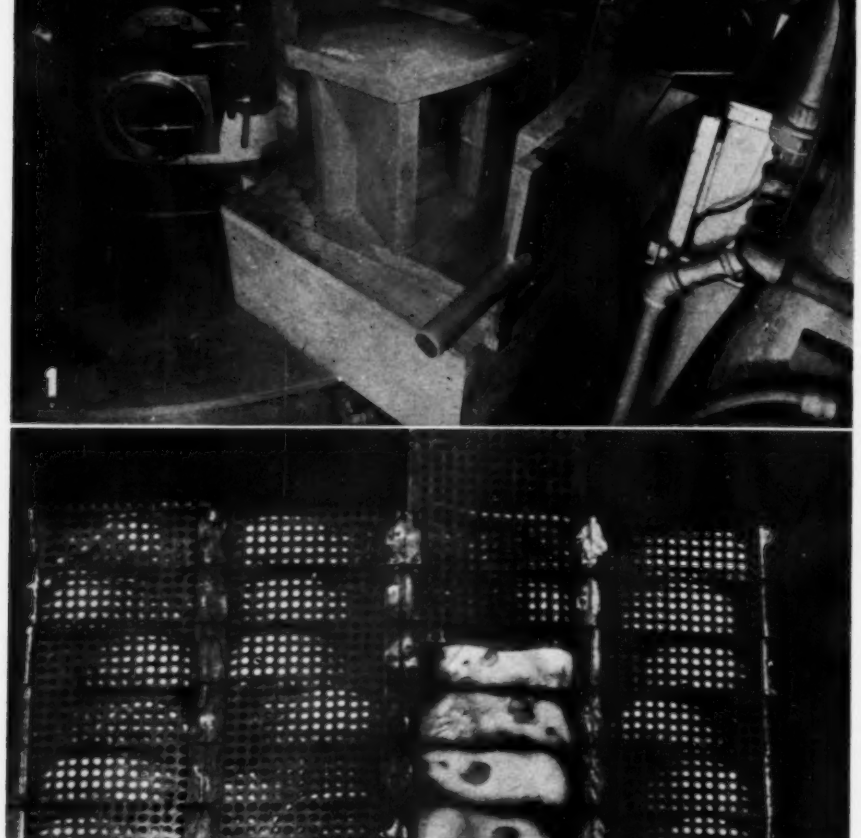

Fig. 1. View of irradiation chamber from the rear. The door has been opened to show the position of the cage containing the mice. The neutron source is on the left.
Fig. 2. Back view of one of the irradiation cages. One of the doors of perforated copper is lifted to show the position of the mice.

thickness. The cages were placed in the box against a brass guide bar (bent on an arc with a radius of 28 inches) which held them 1 inch away from the lead in front, sides, and back. The inside dimensions were 8 inches in height, 26 inches in width,

TABLE I: NUMBER OF MICE SURVIVING 30 DAYS AFTER A SINGLE EXPOSURE TO RADIATION (AS FRACTION OF ORIGINAL NUMBER)

Dose in r 30 d./0 day	None 23/24	400 5/5	500 28/29	600 23/34	700 4/29	800 0/24	1000 0/5	1200 0/5		
Dose in "N" 30 d./0 day	None 10/10	30 5/5	40 5/5	60 18/20	70 7/10	80 8/15	90 2/15	100 0/5	120 0/5	150 0/5

and 3 inches in depth. The exposures were regulated according to readings of a monitor which, in turn, was calibrated with a 25-r Victoreen chamber and r meter. The radiation intensity was varied so that the exposure times of the various daily dose groups were of the same order of magnitude. The highest neutron intensity was approximately 1 "N" per minute. The "N" is an arbitrary unit based on the ionization produced in the 25-r Victoreen chamber which we used.[3]

The lead box was large enough to hold two cages (25 animals each). One of the irradiation cages is shown in Figure 2. These cages were made of perforated copper and were divided into compartments just large enough to hold a mature mouse. The top, bottom, and sides were of solid copper approximately 1 mm. thick. Five times a week each control and experimental lot was loaded into its irradiation cage. The twenty cages were carried in a cart to the automobile which transported them to the cyclotron about twenty blocks away. They were in the cages about an hour each treatment day.

The x-ray exposures were done in our laboratory. The radiation was produced at 185 kv. (peak), using filters of 2 mm. Cu + 1 mm. Al at a distance of 56 cm. The intensity was usually 10 r per minute. The field was about 10 cm. in diameter and the mice were in a circular plastic box during the exposure. The radiation was measured in air, in the center of the container, with the same Victoreen r meter and 25-r chamber as were used for the neutron measurements.

[3] It should be noted that the unit (n) used by other workers is generally based on ionization in a 100-r Victoreen chamber. In general, the two do not agree (for neutron radiation) and there may be considerable variation from one chamber to another even when the size is the same.

PRELIMINARY EXPERIMENTS

Previous investigations, by J. H. and E. O. Lawrence (2–5), had shown that neutron radiation was three to four times more effective than x-rays in reducing survival of mice and rats. It was advisable, however, to determine, in preliminary experiments, the relative effectiveness of neutrons from our source, and of x-rays, upon our animals. The information so obtained would aid in selecting the doses for the experiments on effects of chronic exposures to neutrons.

Acute Exposures: The plan of these experiments is given in Table I, which shows the exposures employed, and the number of animals surviving as a fraction of the original number.

These data are plotted in Figure 3, the upper graph showing the number surviving in percentage of that of controls. An exposure of 600 r resulted in a survival of 65 per cent and one of 700 r gave a value of 15 per cent. By interpolation, 630 r would be expected to kill 50 per cent. The median lethal dose in "N" was 78, and these M.L. doses gave a ratio (in effectiveness) of 8.1 r = 1 "N."

The effect of the two radiations in reducing the mean survival time is shown in the lower graph (Fig. 3). In this respect, 700 r = 86 "N" or 8.1 r = 1 "N."

Some of the effects on the blood are shown in Figure 4. As a ratio of 8.1 r = 1 "N" was indicated, it would be expected that an exposure of 500 r would be intermediate, in this respect, between 60 "N" and 70 "N." The effects of these doses on the total leukocyte counts are shown in the upper graph. The effects of other exposures of roentgen and of neutron radiation also indicated that the relative effects on the leukocyte count agreed with the ratio 8.1 r = 1 "N." Effects of these radiations

on the hemoglobin values are shown in the lower graph of Figure 4. The effect of 70 "N" was intermediate between that of 500 r and of 600 r. These data, together with results of blood counts at other dose levels, indicated that relative effects of the two radiations on the blood agreed with the effects on survival.

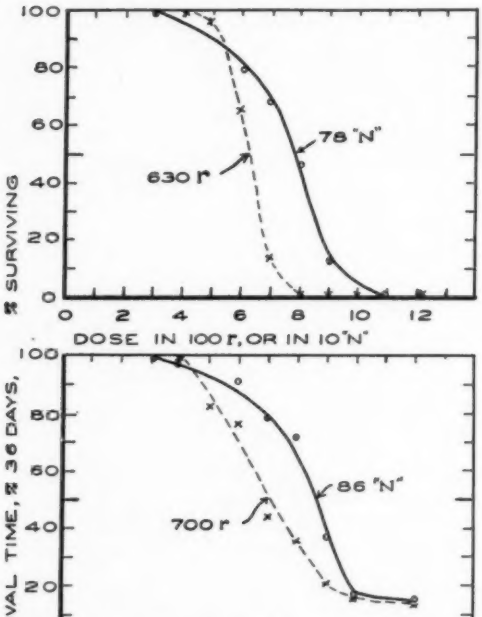

Fig. 3. Graphs showing the relative effects of neutrons and x-rays in single exposures.
Upper graph: The number of animals surviving, in percentage of that of controls, after different amounts of irradiation.
Lower graph: The exposure dose is plotted against the mean survival time of the irradiated animals (percentage of controls). The duration of the experiment was thirty-six days.

Subacute Exposures: The next preliminary experiment was designed to test this ratio of x-ray to neutron effectiveness by comparing effects of a certain dose of neutrons with those of a dose of x-rays which was eight times greater. It was also desired to see if this ratio would hold for multiple exposures. The effects of a daily dose of 10 "N" were compared with those of 80 r per day. Swiss mice were used, and

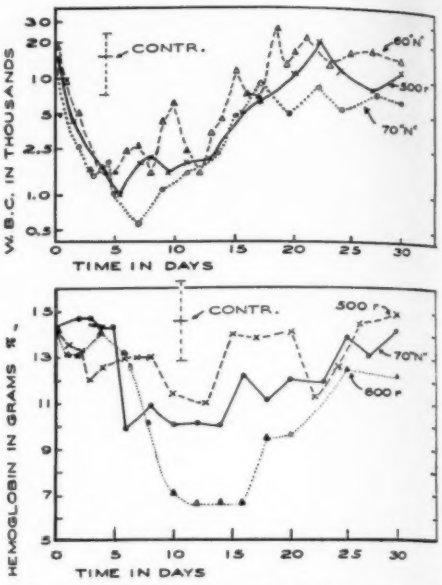

Fig. 4. *Upper graph:* Total leukocyte count (logarithmic scale) of animals receiving a single exposure of 500 r compared to that of one group exposed to 60 "N" and another group receiving 70 "N" in a single treatment. The mean W.B.C. and the standard deviation of control counts during the thirty days are shown in the upper left hand corner.
Lower graph: The hemoglobin, in grams per 100 c.c. of blood, of animals receiving a single exposure of 70 "N" compared to that of animals receiving 500 r in one instance and 600 r in another.

each experimental lot consisted of 25 males and 25 females. One lot of controls (both male and female) made the daily trip (six times a week) to the cyclotron with the animals receiving the neutron radiation, and another lot of controls (both male and female) remained in our laboratory, as the roentgen irradiations were done there. No difference was noted between the two control groups.

The effects of the radiations on survival are shown in the two upper graphs of Figure 5. It will be seen that the exposure of 80 r per day reduced the number surviving to 50 per cent of the original number as follows: males, 19 days; females, 25 days. The median lethal time (M.L.T.) for the entire roentgen-irradiated group was approximately 22 days. In the neutron-irradiated groups, the females died first and the M.L.T. for the whole group was about 23 days. The effect on survival was then

considered to be about the same for 80 r per day as for 10 "N" per day.

The effects of the two types of radiation on the leukocyte counts are shown in the lower graph of Figure 5. The white cell count was reduced within a few days after the exposures had begun, and continued to decrease as the experiment progressed.

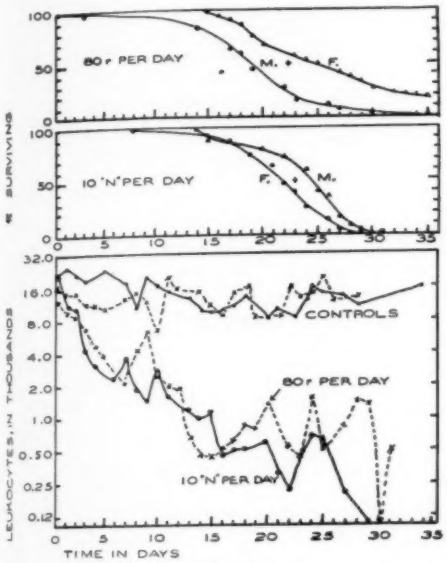

Fig. 5. *Upper graph:* Effect of 80 r per day on survival of mice (one group of males and one group of females), and effect of 10 "N" per day on a similar group of animals.
Lower graph: Effects of 80 r per day on the leukocyte count compared to effects of 10 "N" per day.

The exposures were stopped after the twenty-fifth day of irradiation, as over half of the original number of animals in the experimental lots had died. The effect of 10 "N" per day in the production of leukopenia was similar to that of 80 r per day. Other effects on the blood were also pronounced, and the amount of injury was about the same with either type of radiation. The lowering of the erythrocyte number is shown in the upper graph of Figure 6, and the reduction in hemoglobin is indicated in the lower graph. The red cell counts and hemoglobin values in the experimental animals remained within normal limits for about a week and then dropped steadily as the irradiations continued. The slope of the curves for 10 "N" per day was approximately the same as for the daily exposure of 80 r.

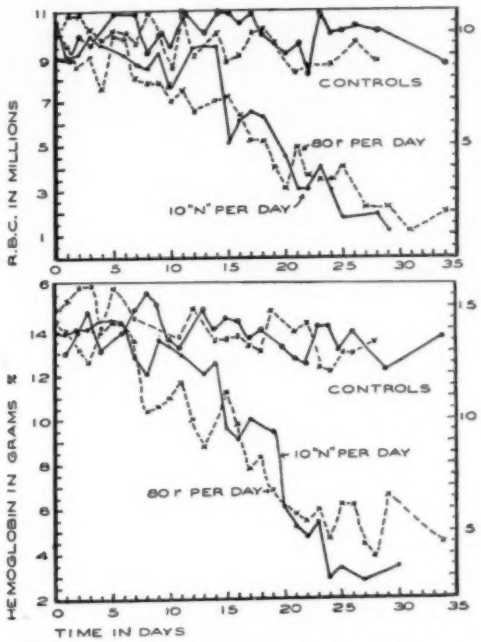

Fig. 6. *Upper graph:* Effects of 80 r per day on the erythrocyte count compared with similar effects of 10 "N" per day.
Lower graph: Hemoglobin concentration of blood of animals exposed to 80 r per day compared to that of animals receiving daily doses of 10 "N" per day.

Damage to the gonads, spleen, bone marrow, and intestine was heavy, especially toward the end of the irradiation period. As near as one could judge on the postmortem material, the injury produced by 10 "N" per day was qualitatively and quantitatively similar to that of 80 r per day.

EFFECTS OF SMALL DAILY DOSES ("CHRONIC EXPOSURES") OF FAST NEUTRONS

Plan of Experiments: Results of the experiments using single ("acute") exposures indicated that the fast neutrons were as effective as eight times as much roentgen radiation (measured with our 25-r Victoreen ionization chamber). Effects of moderately heavy ("subacute") daily doses also indicated an equivalence of 80 r and 10 "N." The next question under considera-

TABLE II: EFFECTS OF SMALL DAILY DOSES OF FAST NEUTRONS

Strain	Sex	Total "N"	Irradiation Period in Weeks	Number Surviving at End of Irradiation Period, of Original Twenty-five
Swiss	Male	None (Controls)	90	5
Swiss	Female	None (Controls)	89	6
				5.5 = av.
CF_1	Male	None (Controls)	83	4
CF_1	Female	None (Controls)	83	7
				5.5 = av.
		(Dose 1, 0.014 "N" per day, 0.07 "N" per week)		
Swiss	Male	6	90	4
Swiss	Female	6	89	10
				7 = av. (127% of control value)
CF_1	Male	6	83	5
CF_1	Female	6	83	8
				6.5 = av. (118% of control value)
		(Dose 2, 0.07 "N" per day, 0.35 "N" per week)		
Swiss	Male	30	90	4
Swiss	Female	30	89	6
				5 = av. (91% of control value)
CF_1	Male	29	83	1
CF_1	Female	29	83	5
				3 = av. (55% of control value)
		(Dose 3, 0.14 "N" per day, 0.7 "N" per week)		
Swiss	Male	60	90	1
Swiss	Female	60	89	3
				2 = av. (36% of control value)
CF_1	Male	57	83	1
CF_1	Female	57	83	5
				3 = av. (55% of control value)
		(Dose 4, 1.4 "N" per day, 7.0 "N" per week)		
Swiss	Male	235	34	11
Swiss	Female	228	33	12
				11.5 = av. (49% of control value)
CF_1	Male	162	24	7*
CF_1	Female	162	24	10*
				8.5 = av. (37% of control value)

* Survival of controls at this time = 23.3/25 (av.).

tion was what doses of fast neutrons to use in the long-term ("chronic") experiments. The daily maximum permissible exposure to x-rays has been considered as 0.1 r per day, or 0.55 r per week (1). Obviously, an exposure thought to be equivalent to this value should be included in the neutron experiments. As it was planned to irradiate the animals five times a week, the lowest daily dose was set as 0.014 "N" per day or 0.07 "N" per week. Daily exposures of 10 "N" produced injury so rapidly that about one-tenth of this (1.4 "N"/day) seemed to be adequate for the highest dose. This was expected to have about the same effect as 11 r per day, and Henshaw (6) had found that daily doses of 5 r and 10 r definitely reduced survival time.

Twenty-five animals of each group (Swiss, male; Swiss, female; CF_1, male; CF_1, female) were used for the controls and for each of the experimental lots (0.014 "N"/day; 0.07 "N"/day; 0.14 "N"/day; 1.4 "N"/day).

Survival: The dose of 1.4 "N" per day definitely reduced survival of mice of both strains and both sexes. This exposure was discontinued when the number of survivors was reduced to less than 50 per cent of that of controls. The other exposures were continued until survivors in the 0.14 "N" per day group had been reduced to less than 50 per cent of controls. At this time, the other dose groups as well as the control groups contained less than half of the original number of animals. The total exposure, the irradiation period, and number of animals surviving at the end of each experiment are shown in Table II.

It will be seen from this table that the time for 39 of the original 50 controls to die was about 90 weeks for the mice of

the Swiss strain, and 83 weeks for those of the CF_1 strain. At this time the number of animals in the Dose 1 groups was slightly higher than in the control lots. The number of survivors in the Dose 2 groups was slightly less than that of the controls, and that of the Dose 3 lots was definitely reduced. The number surviving in the Dose 4 group is not to be compared to that of the other lots, as the irradiation period, ended when the number surviving had been reduced to 50 per cent of controls, was much shorter.

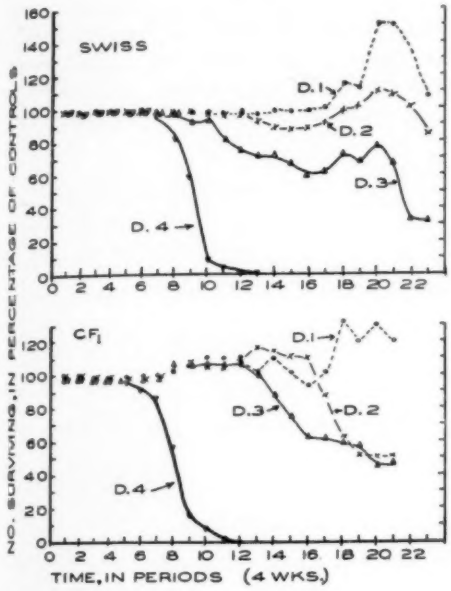

Fig. 7. Number of animals surviving, in per cent of that of the controls, plotted against time. O = Dose 1, 0.014 "N" per day. X = Dose 2, 0.07 "N" per day. Δ = Dose 3, 0.14 "N" per day. ∇ = Dose 4, 1.4 "N" per day.

Upper graph: Animals of the Swiss strain. Twenty-five males and 25 females, in each experimental lot, at the beginning of the experiment.

Lower graph: Animals of the CF_1 strain. Number at the beginning of the experiment same as above.

The number surviving (in per cent of controls) at different times is shown in Figure 7. The CF_1 animals of the Dose 4 group died before those of the Swiss strain. In the Dose 3 lots, the Swiss animals were reduced in number before those of the CF_1 strain. In the Dose 2 groups, the CF_1 animals were reduced in number before those of the Swiss strain.

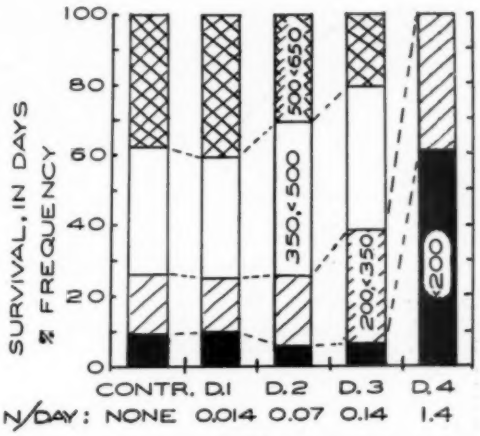

Fig. 8. Frequency of different survival times of animals in the control and irradiated groups. The frequency, in percentage, of occurrence of animals with survival times below 200 days is indicated by height of the solid black columns. The relative frequency of survival times between 200 and 350 days is shown by the extent of the singly cross-hatched areas. Frequency of survival times between 350 and 500 days is indicated by the unshaded areas, and that for 500 to 650 days is indicated by the doubly cross-hatched areas. The frequency is in percentage of 100 animals (both strains and both sexes) for each control and experimental lot.

Considering the entire group of 100 animals (both strains, both sexes), the frequency of certain survival times is shown in Figure 8. As regards decrease of survival, Dose 1 seemed to be ineffectual. Dose 2 seemed to have reduced only the older age (> 500 days) group. With Dose 3 the number of animals of 350–500 days and also >500 days was reduced. The pronounced effect of Dose 4 is evidenced by the great increase in the number of animals living less than 200 days and of those living less than 350 days.

In Figure 9, the time required for 50 per cent of the original number to have died (L.T. 50) is plotted against the daily dose. These data are for all 100 animals of each exposure group, and the L.T.50 is expressed in percentage of control value. The mean survival time (in percentage of controls) is also given in this figure. The results of these two methods of plotting effects on survival agree closely. Effects of 10 "N" per day and of a single dose of 100 "N"

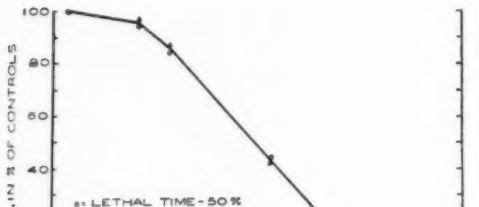

Fig. 9. Survival at different daily doses as indicated by: O, the time required to reduce the number of survivors to 50 per cent of that at the beginning of the experiment, and Δ, the mean survival time of all the individuals receiving a given dose, expressed in percentage of the mean value for control animals.

have been included to show extreme values.

The actual mean survival times are shown in Table III. The animals of the Swiss strain lived longer than those of the CF_1 strain, but the relative effects of the different doses on the M.S.T. were approximately the same for both strains. Doses 1 and 2 did not reduce the M.S.T., but it was shortened by the Dose 3 exposure by about eight weeks. The Dose 4 M.S.T. was less than half that of the controls.

Effects on the Hemopoietic System: The effect of the radiation on the leukocyte count is shown in Figure 10. Each point is the average value for 32 to 48 counts on animals of all four groups taken during a period of four weeks. Animals with a leukemoid blood picture (or white cell count above 30,000) have not been included and will be discussed elsewhere. It will be seen from the figure that the leukocyte values with Doses 1, 2, and 3 do not reach leukopenic levels, but that the mean values are below that of the controls. It was thought of interest to demonstrate the leukocyte range that was most frequently involved in this decrease. In Figure 11 it may be seen that the frequency of counts above 15,000 was decreased even in the Dose 1 group and that this decrease was only slightly greater for the higher dose groups. The frequency of counts be-

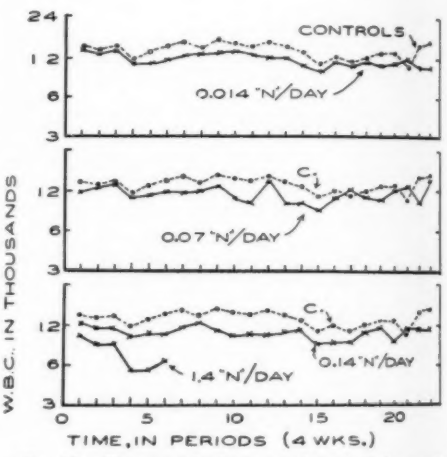

Fig. 10. The mean leukocyte value of all the counts taken in a period of four weeks is plotted, on a logarithmic scale, against time in periods of four weeks each.

TABLE III: MEAN SURVIVAL TIMES

(25 Males and 25 Females in Each Group)

	Controls	Dose 1	Dose 2	Dose 3	Dose 4
Swiss strain:					
M.S.T. (days)	475	470	443	392	206
M.S.T. (%)	100	99	94	83	43
CF_1 strain:					
M.S.T. (days)	420	397	412	377	168
M.S.T. (%)	100	95	98	88	40

(100 Animals, Both Strains and Both Sexes, in Each Group)

Dose Group	"N"/day	M.S.T. in Weeks	Standard Deviation	Standard Error of Mean	Diff. from Control / Standard Error
Control	None	62	22	2.2	...
Dose 1	0.014	62	16	1.6	...
Dose 2	0.07	60.6	20	2.0	0.05
Dose 3	0.14	54	20	2.0	2.7
Dose 4	1.4	26.6	9.6	0.96	15.5

low 5,500 increased only slightly with Doses 1, 2, and 3 but was quite evident in the Dose 4 animals. Therefore, the most evident effect of the chronic irradiations (of less than 1.4 "N" per day) was an increase in frequency of white cell counts below 15,000.

The mean value of percentage of lymphocytes seemed to be lower than in the controls, even in the Dose 1 and 2 groups in some periods. Considering counts over the entire experiment time, the only significant change was in the Dose 4 group, in which there was an increase in frequency in the counts below 25 per cent and also below 50 per cent. There was a slight increase in frequency of counts below 76 per cent even with Doses 3 and 2 but not with Dose 1 (Fig. 12). Progressive changes in the differential leukocyte picture occurred in the Dose 4 (1.4 "N" per day) group. The effect on percentage of lymphocytes at different times in the various dose groups is shown in Figure 13. No definite "shift to the left" was observed except in the animals receiving 1.4 "N" per day, and this was apparent only after most of the animals had died. As this "shift" concerned the immaturity of only the heterophils (neutrophilic granulocytes), the relative number of "juvenile" and "band" forms was later calculated as percentage of total heterophils. This percentage was determined from twenty-five blood counts near the close of the irradiation period. This was done for all four groups, making a total of 100 counts per control and experimental group. The results are shown in Table IV.

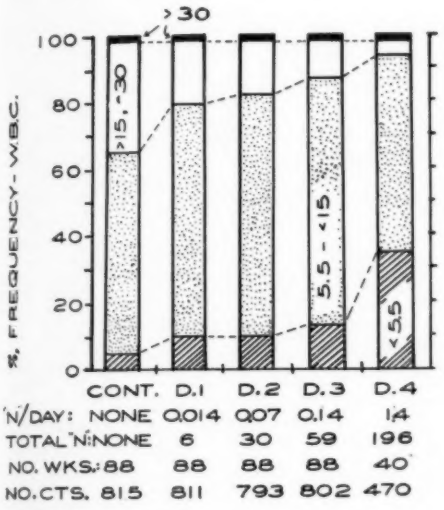

Fig. 11. Relative frequency of different leukocyte counts. The range of leukocyte counts, in thousands, is indicated for each class (distinguished by type of shading). For example, in the control group 5 per cent of the counts were in the range from 0 to 5,500 (diagonal lines). Sixty-five per cent were below 15,000; 60 per cent were in the class covering the range from 5,500 to 15,000 W.B.C. (stippled region).

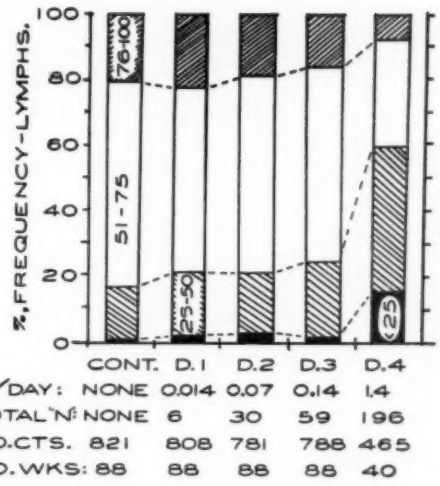

Fig. 12. Relative frequency of different classes of lymphocyte counts. Solid black area: lymphocyte counts below 25 per cent of total W.B.C. Lines down to right: per cent counts between 25 and 50. Open columns: counts between 51 and 75, inclusive. Lines up to right: counts above 75.

TABLE IV: NUMBER OF IMMATURE FORMS IN PERCENTAGE OF TOTAL NUMBER OF HETEROPHILS

	Controls	Dose 1	Dose 2	Dose 3	Dose 4
"N" per day	None	0.014	0.07	0.14	1.4
Mean value	7.5	7.8	7.0	7.0	12.5
Standard error of mean	0.8	1.25	1.2	1.0	2.1

Although the mean values with Doses 1, 2, and 3 were practically the same as that of the controls, a few high values were obtained in these irradiated groups. In the Dose 4 group, the mean number of immature forms was definitely higher than that

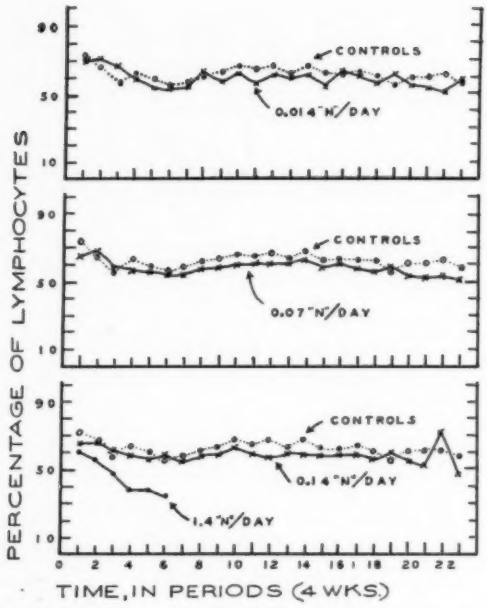

Fig. 13. The mean number of lymphocytes (relative to the total leukocytes) per period of four weeks is plotted against time for the various dose groups.

of the controls. In five of the counts of the Dose 4 group (animals surviving L.D. 50), the number of immature forms was above 70 per cent of all of the heterophils.

There was no definite reduction in the number of erythrocytes during the period of irradiation. Several animals of the Dose 4 group survived after the irradiation period had ended and these later suffered a reduction in the red cell count and in hemoglobin. The results of the red cell and hemoglobin studies are shown in Tables V and VI.

Determinations of platelet number, of percentage of reticulocytes, and of clotting time were done near the end of the irradiation period. Results of these tests were essentially the same for the irradiated as for the control animals. These tests were repeated on a new lot of animals receiving 1.4 "N" per day and the results are shown in Table VII, together with those of other tests. The platelet count was not reduced by the radiation and the clotting time was not prolonged. In fact, these values were sometimes better than the mean of the control group. There was a somewhat progressive increase in percentage of reticulo-

TABLE V: MEAN VALUE OF RED CELL COUNTS (IN MILLIONS), IN ALL FOUR ANIMAL GROUPS, TAKEN DURING A PERIOD OF FOUR WEEKS

Periods	Controls	Dose 1, 0.014 "N" per Day	Dose 2, 0.07 "N" per Day	Dose 3, 0.14 "N" per Day	Dose 4, 1.4 "N" per Day
1	10	10	9.8	9.8	9.9
2	9.9	9.8	9.7	10.2	9.6
3	10	10	9.9	10.1	9.9
4	9.2	9.4	9.8	9.7	8.8
5	9.3	9.2	9.8	9.6	8.7
6	9.4	9.2	9.2	10.1	9.1*
7	9.2	9.2	9.2	9.2	8.7*
8	8.3	9.2	9.9	9.5	8.0
9	8.8	8.8	9.2	9.3	7.6
10	8.7	9.1	8.7	8.5	7.3
11	8.5	8.2	8.9	8.0	5.0
12	8.6	8.1	8.6	8.3	
13	8.5	8.8	8.8	8.2	
14	8.0	8.4	9.4	8.7	
15	8.1	8.3	9.1	7.7	
16	8.1	8.4	7.9	7.1	
17	8.2	8.2	8.7	7.8	
18	8.2	8.4	9.2	7.5	
19	8.1	8.1	8.7	7.3	
20	7.9	8.1	10.4	7.9	
21	8.4	8.4	9.6	7.4	
22	7.3	7.8	10	8.0	
23	7.3	6.8	9.9	6.6	

* End of Dose 4 irradiation period.

TABLE VI: HEMOGLOBIN DETERMINATION (IN GM. PER CENT): MEAN VALUE FOR ALL FOUR ANIMAL GROUPS, TAKEN DURING A PERIOD OF FOUR WEEKS

Periods	Controls	Dose 1, 0.014 "N" per Day	Dose 2, 0.07 "N" per Day	Dose 3, 0.14 "N" per Day	Dose 4, 1.4 "N" per Day
1	14	14.2	14.5	14.1	14
2	14.3	14.7	14.2	14.7	15.1
3	14.5	14.9	14.3	14.7	15.2
4	14.4	14.5	14.3	14.6	15
5	14.3	14.2	14.5	14.7	14.4
6	14.8	15	14.4	14.8	14.9*
7	14.5	14	13.9	14.5	13.5*
8	14.1	14.5	14	14.5	12.6
9	15.0	14.5	14.5	14.0	11.7
10	13.6	14.3	13.9	13.8	9.3
11	14.3	13.8	13.8	13.9	7.5
12	13.6	13.5	14.0	13.3	
13	14.1	14.8	13.9	13.6	
14	13.5	13.1	13.3	12.7	
15	14	18.1	14.0	13.4	
16	13.5	13.4	12.6	13	
17	12.9	13.5	12.7	12.6	
18	12.9	12.7	12.5	12.7	
19	13.8	13.4	13.1	12.1	
20	13.1	13.5	13.6	12.4	
21	12.8	12.9	13.4	11.3	
22	12.5	13.9	11.9	10.0	
23	12.1	11.4	12.1	11.0	

* End of Dose 4 irradiation period.

TABLE VII: BLOOD STUDIES AND OTHER OBSERVATIONS ON ANIMALS RECEIVING 1.4 "N" PER DAY: VALUES IN PERCENTAGE OF CONTROLS

(8 Counts per Period)

Period (4 wk.)	Platelets	Reticulocytes	Clotting Time	White Cells	Per Cent Lymphocytes	Weight	Per Cent Surviving
1	126	107	...	70	82	90	100
2	98	113	...	46	86	88	92
3	176	98	...	71	83	85	82
4	84	94	86	41	83	75	75
5	61	131	99	63	66	75	75
6	123	176	118	36	73	75	56
7	116	136	80	37	53	75	50
8	116	116	88	62	50	71	33

cytes during irradiation but the effect was not pronounced even at the time that survival had been reduced to 35 per cent. In contrast, the white cell count, percentage of lymphocytes, weight, and survival values showed progressive injury with time.

Terminal Blood Picture: Many of the animals had blood counts taken only a few days before they died or were killed. The most definite finding was leukopenia in animals receiving Doses 2, 3, and 4. Animals of the Dose 4 group were also anemic to some extent. These results are shown in Tables VIII and IX. The histologic condition of the bone marrow at autopsy was that of slight hypoplasia in animals of Dose 3 and Dose 4 groups. In a few instances, hyperplasia occurred in animals receiving Doses 3 and 4.

TABLE VIII: TERMINAL BLOOD PICTURE
(Percentage Occurrence of Different Conditions)

Condition	Controls	Dose 1, 0.014 "N" per Day	Dose 2, 0.07 "N" per Day	Dose 3, 0.14 "N" per Day	Dose 4, 1.4 "N" per Day
"Normal"	88	85.5	70.5	68	9.1
Inflammation	5.5	7.9	6.8	2.5	0
Anemia	4.5	2.2	5.7	3.4	13.2
Leukopenia (WBC 22,500)	1.0	4.4	14.8	20.7	76.5
Leukemoid hyperplasia	1.0	0	2.2	3.4	1.2
No. animals	90	89	88	87	76

TABLE IX: CONDITION OF THE BONE MARROW AT AUTOPSY

(Percentage Occurrence of Different Conditions)

Condition	Controls	Dose 1, 0.014 "N" per Day	Dose 2, 0.07 "N" per Day	Dose 3, 0.14 "N" per Day	Dose 4, 1.4 "N" per Day
"Normal"	89	89	83.5	56	26.8
Hypoplasia	4.9	4.6	6.2	25.4	61.0
Hyperplasia	3.1	4.6	6.2	14.6	9.7
Lymphocytic involvement	3.0	1.5	3.1	4.0	2.5
No. animals	63	66	66	75	82

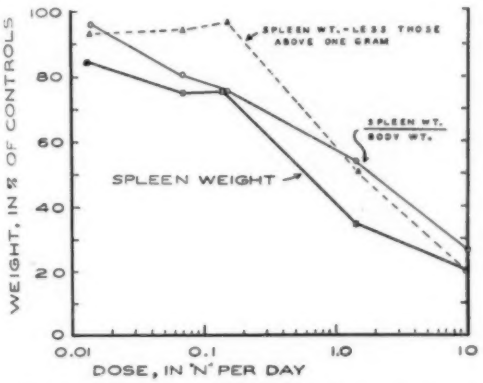

Fig. 14. The mean weight of the spleen, at autopsy, plotted against dose in "N" per day. In addition to the actual spleen weight, its value relative to the total body weight is shown in the second curve. The other curve indicates the weight value after the spleens weighing more than one gram have been omitted.

Effects on the Spleen: The spleens were weighed at autopsy and the mean value was determined for each dose (about 80 animals each). The mean weights of the spleens, in percentage of the control value, are shown in Figure 14. The spleen weight, relative to that of the controls, was reduced to some extent by even the smallest dose. When the ratio of spleen weight to body weight was plotted, the difference between the irradiated and control groups was slightly reduced. These curves do not

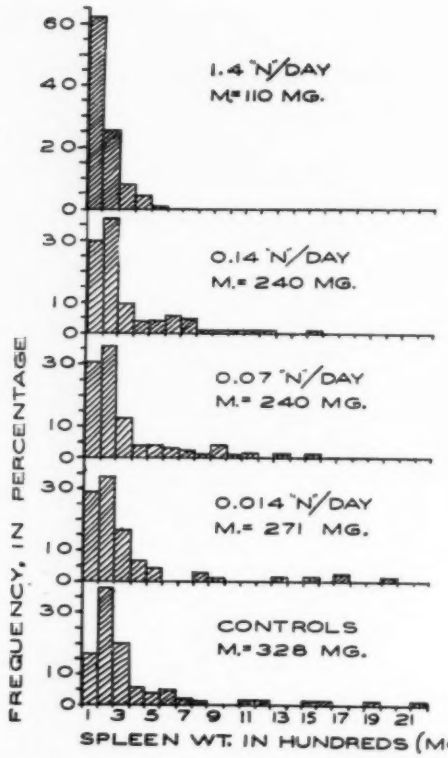

Fig. 15. Graph showing frequency of different weights of spleens (classes of 100 mg.) in the control and irradiated lots.

TABLE X: HISTOLOGIC APPEARANCE OF SPLEEN AT AUTOPSY

(Percentage Occurrence of Different Conditions)

Condition	Controls	Dose 1, 0.014 "N" per Day	Dose 2, 0.07 "N" per Day	Dose 3, 0.14 "N" per Day	Dose 4, 1.4 "N" per Day
"Normal"	77.5	77.4	75.8	48.5	29.7
Hypoplasia	0	5.3	6.9	28.2	61.0
Hyperplasia (inflammatory)	12.3	5.3	5.2	6.1	3.0
Neoplasia (?)	10.2	12	12.1	17.2	6.3
No. animals	57	75	58	64	64

represent the relative reduction of normal spleen tissue only, since several hyperplastic spleens are included in each group (except for Dose 4). The hyperplastic spleens were largest, though not more numerous, in the control groups (Fig. 15). When the hyperplastic spleens (above 1 gm.) are omitted, the relative effect of the radiation is greatly reduced (Fig. 14).

TABLE XI: MEAN BODY WEIGHT, ALL FOUR GROUPS OF ANIMALS, PER PERIOD OF FOUR WEEKS

Period	Controls	Dose 1, 0.014 "N" per Day	Dose 2, 0.07 "N" per Day	Dose 3, 0.14 "N" per Day	Dose 4, 1.4 "N" per Day
1	21.5	23.3	22.4	23.4	22.2
2	25.7	26.4	25.0	25.9	24.2
3	26.6	27.2	26.9	26.8	24.2
4	27.3	27.0	25.2	26.6	24.2
5	29.5	28.1	28.7	28.0	23.6
6	28.6	29.1	27.5	28.5	24.2*
7	28.9	29.4	28.9	29.5	22.0
8	29.5	29.5	29.8	29.5	23.1
9	28.7	31.4	27.7	29.5	22.5
10	31.3	30.4	30.2	29.8	20.5
11	30.3	30.8	29.2	29.3	18.5
12	31.0	30.9	29.9	29.7	
13	30.2	30.8	30.0	28.1	
14	30.2	30.1	28.9	27.8	
15	30.7	30.4	28.2	27.2	
16	30.0	30.1	29.4	25.2	
17	29.2	28.1	30.7	26.1	
18	29.7	30.1	31.2	27.2	
19	29.8	28.6	29.4	25.4	
20	27.8	27.6	26.6	26.1	
21	28.4	28.1	27.4	26.8	
22	29	29.8	29.5	28.5	
23	28.4	29.5	26.8	27.8	

* End of Dose 4 irradiation period.

The only histologic evidence of radiation damage to the spleen was hypoplasia. Splenic activity was reduced to some extent in a few animals of the Dose 3 group, and the majority of those of Dose 4 showed evidence of moderate radiation injury (reduction in size and number of lymphoid follicles, presence of injured cells, increased phagocytosis, and relative increase in fibrous elements). The results are summarized in Table X.

Effect on Body Weight: The mean weight of all the animals taken at the end of each period is shown in Table XI. Body weight was affected only in the Dose 4 animals, and represented a failure to gain rather than actual loss during the irradiation period. Animals of Dose 4 groups which survived after the irradiation period eventually became emaciated and had definitely lost weight.

Effects on the Eye: The eyelids and lashes were not noticeably affected by the radiation. Some of the lids became infected, but with no greater frequency than

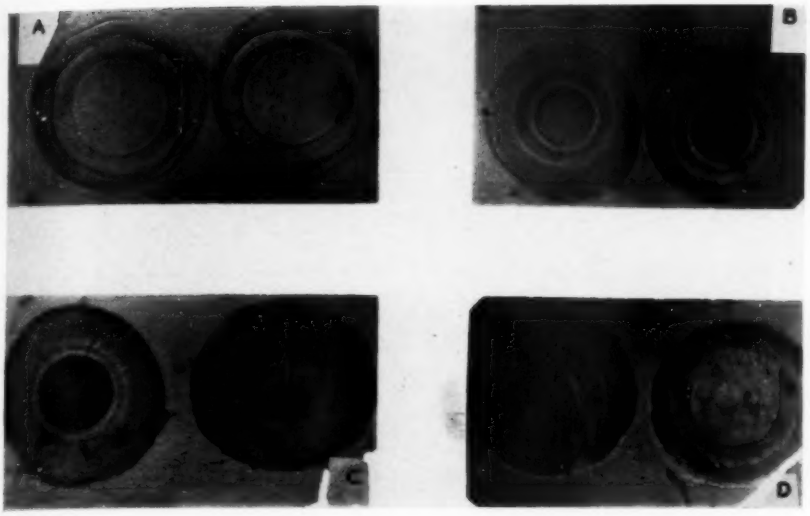

Fig. 16. Photomicrographs of lens whole mounts in balsam. The relative diameter of the various layers may be seen. A. Controls. B. From an animal of the Swiss strain, exposed to 1.4 "N" per day, near L.T. 50. It will be seen that the diameter of the nucleus is relatively smaller than in the control lens. C. From an animal of the hybrid strain exposed to 1.4 "N" per day, near L.T. 50. D. From an animal of the Swiss strain exposed to 11 r per day, L.T. 50. It will be seen that the effect on the nuclear diameter is not as pronounced as in those exposed to 1.4 "N" per day.

for the controls. Corneal opacities developed in some of the animals, but these occurred with about the same frequency in the controls and were due, apparently, to infection, etc. The lens, however, was definitely affected by the radiation. All of the Dose 4 animals surviving the irradiation period became blind. This condition was due to opacity of the lens, as examination by an ophthalmologist[4] and histologic study revealed no other apparent abnormality of the eye. The cataracts did not form rapidly but, by the time half of the irradiated animals had died, the survivors had visible opacities in the lens. The lenses were studied in four ways (1) gross examination, (2) ability of the excised lens to transmit and focus a beam of light on photographic paper, (3) histological examination of thin sections, and (4) microscopic examination of a whole mount after dehydration and clearing. Grossly, the lens appeared to be cloudy, and in some cases chalky white. A clear lens focussed a beam of light on photographic paper placed directly underneath, and the developed picture showed a sharply outlined black spot in the center of the image. The image produced by a lens with cataract appeared cloudy, or was completely blank. In microscopic section, the lens with cataract showed degeneration of the epithelium and autolysis of lens fibers. The cleared lens, whole mount, demonstrated the various layers very well. In the controls the diameter of the central ring, or nucleus, was about half of that of the entire lens. In the lenses with cataract, the nucleus was reduced in diameter and in some instances the surface was opaque to light. Also the rings around the nucleus differed in relative diameter from those of the controls. Some of these preparations are shown in Figure 16.

The frequency of cataract in the different groups is shown in Table XII, together with data indicating the decrease in diameter of the nuclear portion of the lens in the Dose 4 animals.

[4] The author is indebted to Dr. Ludwig von Sallmann, Department of Ophthalmology, for making these examinations.

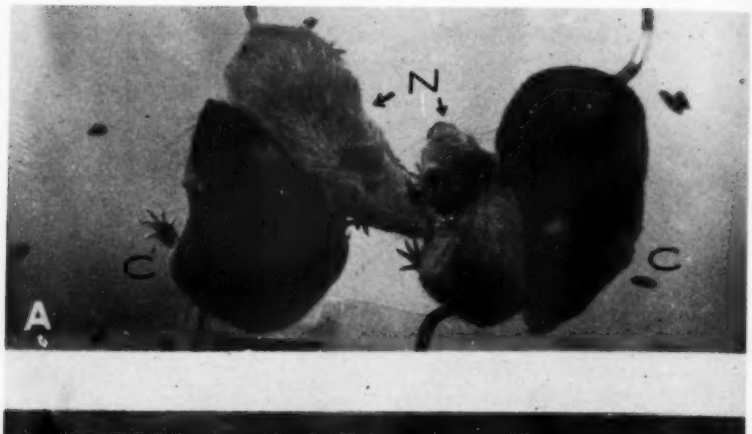

Fig. 17. Effects of 1.4 "N" per day on depigmentation of hair.
A. Two controls (C) and two irradiated (N) hybrid animals 28 weeks after the beginning of the experiment. The irradiated animals were exposed to 1.4 "N" per day and had received a total of 171 "N" at this time. All control and experimental animals were black at the beginning of the experiment. It may be seen that the hair of the irradiated animals has become lighter in color. These animals are representative of their respective groups.
B. After 34 weeks of irradiation (1.4 "N" per day). The experimental mice have received a total of 238 "N." The hair of the irradiated animals may be seen to be almost entirely unpigmented. The eye color has not been affected.

The Dose 4 experiment (1.4 "N" per day) was repeated using 25 Swiss and 25 hybrid (Swiss × C_{57} black) animals. Seventy per cent of the eyes of Swiss animals eventually had visible cataracts and 50 per cent of the pigmented eyes became similarly affected. Eyes were studied in an additional experiment using 17 Swiss animals. Again, the frequency of visible cataracts was high (50 per cent at L.T. 50).

Effect on the Hair: Although no quantitative studies of epilation were made, it was evident by the end of the experiment that some epilation had occurred in the Dose 4 animals. The loss of hair was most noticeable in the frontal and nasal regions of the head, and in the thoracic region of the body. In the Dose 4 experiment, using black hybrid animals, a definite loss of pigment was evident in the hair of the irradiated mice (Fig. 17).

Effect on Estrus in the Female: A few females of the Dose 4 group survived after the end of the irradiation period. These were placed with fertile males, but no pregnancies resulted. These irradiated females were found to be in constant anestrus.

Estrous tests were then begun on animals of control and Dose 3 groups. Later, tests were made on Dose 2 and Dose 1 animals. Results of these tests are shown in Figure 18. In the Swiss animals, the controls ran regular estrous cycles for about sixty-five weeks, but toward the end of the

TABLE XII: NUMBER OF EYES WITH VISIBLE CATARACT
(50 Eyes in Each Group, *i.e.*, 200 for Each Dose)

Animals	Controls	Dose 1, 0.014 "N" per Day	Dose 2, 0.07 "N" per Day	Dose 3, 0.14 "N" per Day	Dose 4, 1.4 "N" per Day
Swiss males	0	0	0	0	14
Swiss females	0	0	0	1	18
CF_1 males	0	0	0	0	6
CF_1 females	0	0	0	4	14
Totals	0 0*	0 2*	0 7*	5 23*	52†
Percentage	0 0*	0 8*	0 32*	2.5 85*	26†
Mean ratio of diameter of nucleus to lens	0.55 0.52‡	0.54 ...	0.54 ...	0.53 ...	0.38‡

* Based on study by ophthalmologist on animal surviving the L.T. 50.
† All of these eyes at L.T. 50 were so opaque that critical examination with slit lamp was not possible.
‡ From animals of a repeat experiment.

experiment the cycles became less frequent. Tests on the Dose 1 group were not begun until the eighty-second week, and from this time until the end of the experiment the cycle frequency was no lower than that of the controls. Tests were begun on the Dose 2 animals in the sixty-ninth week, and the animals were in constant anestrus by the eighty-fourth week. The Dose 3 animals were in constant anestrus by the eighty-fourth week. The Dose 3 animals were tested from the fortieth week, and by the sixtieth week the frequency of cycles was definitely less than that in the controls. Complete anestrus was not produced until the eighty-fourth week. Animals of the Dose 4 group were tested from the thirty-fourth week until the forty-third, and no estrous cycles were obtained during this period.

The control females of the CF_1 strain exhibited irregular cycles by the sixtieth week and by the seventieth the frequency had become very low. The estrous cycle frequency of the Dose 1 animals was not affected as compared with controls. It is doubtful whether Dose 2 and Dose 3 animals showed any effect on estrus, as by the time their cycle frequency was reduced, that of the controls had become irregular. Dose 3 may have shown some effect, but a few animals recovered near the end of the experiment. Dose 4 animals were tested from the thirty-first to the thirty-eighth week and during this time they were all in constant anestrus.

In repeat experiments, three lots of controls and two receiving Dose 4 were tested for estrous cycles from the beginning of the experiment. The frequency was reduced in the Dose 4 animals by the fifteenth week and all animals were in constant anestrus by the eighteenth.

Histologic Study of the Ovaries: Ovaries of all Dose 4 animals examined were devoid of recognizable germ cells. There were no complete follicles, and the ovaries were fibrotic. Ovaries of Dose 3 animals showed no mature follicles; some contained corpora lutea and many lutein cells. Most of the ovaries showed an increase in fibrous tissue. In some, small follicles were apparently being formed at the periphery but none contained ova. In the Dose 2 group, some ovaries contained follicles with oocytes in different stages of development, but the activity appeared to be less than in the controls. Some ovaries of Dose 1 groups appeared to be less active than the controls. Control ovaries examined early in the experiment contained many follicles in various stages of development, but those examined at the end of the experiment

TABLE XIII: HYPOPLASIA OF OVARY, OOGENESIS

Animals	Controls	Dose 1, 0.014 "N" per Day	Dose 2, 0.07 "N" per Day	Dose 3, 0.14 "N" per Day	Dose 4, 1.4 "N" per Day
No. examined	33	30	26	26	37
Per cent with oogenesis	76	54	31	8	0
Per cent of controls	100	71	41	11	0
Per cent injured	0	29	59	89	100

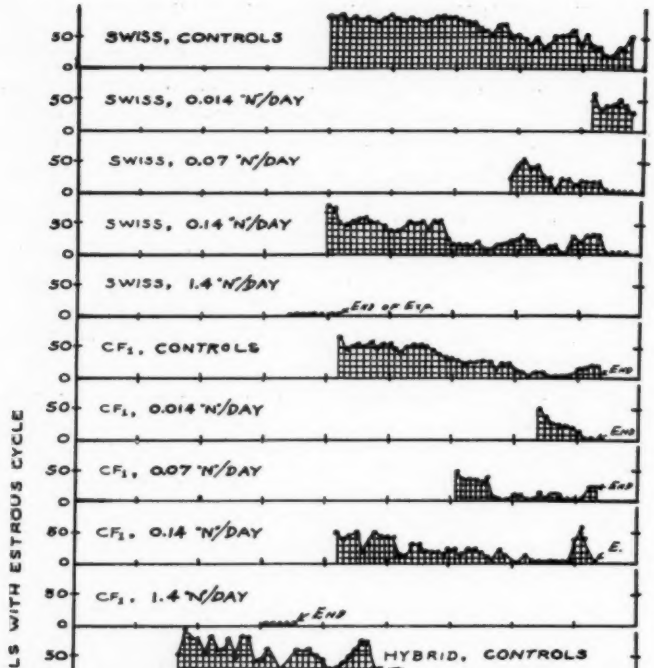

Fig. 18. Percentage of animals, in each group, with an estrous cycle per week. Vaginal smears were made at least four times each week per female, during the test periods. See text for further details and discussion of results.

showed definite signs of senility. The frequency of apparent hypoplasia for all of the animals examined is shown in Table XIII.

Mating Tests with Irradiated Males: CF_1 males of the Dose 4 group were placed with fertile females from the twenty-sixth to the thirty-first week, and no pregnancies resulted. Likewise, the Swiss Dose 4 males were tested during a period of six weeks (thirty-first to thirty-seventh), and the results were also negative. In a repeat experiment, Dose 4 (Swiss) males were tested from the beginning of the experiment and these gave negative mating tests by the fifth week of treatment. In an additional experiment with similar animals, mating tests were negative by the sixth week, there was one litter out of eight tests in the seventh week, and tests were then negative from the eighth week until the end of the experiment (fourteenth week).

The degree of effect of Dose 3 on sterility was questionable. Mating tests on

CF_1 animals from the sixtieth to the seventy-fourth week were negative. However, tests of controls of this strain from the seventy-ninth week to the eighty-fourth gave only one positive of fifteen tests. Males of the Swiss strain (Dose 3) were tested from the fortieth to the eighty-sixth week. These animals continued to give positive results, without reduction in litter size, until the sixty-eighth week. From the sixty-eighth to the eighty-sixth week, litters were produced in 7 of the 60 tests. The average number of offspring per litter (in the 7 positive results) was 6.6. Controls were tested from the eightieth to the eighty-third week. Of the 12 tests, 4 were positive and the average litter size was 6.5.

By the time animals and space were available for tests of Dose 2 and Dose 1 groups, control results were becoming irregular, and results of tests on irradiated animals could not be evaluated. A test of Dose 2 animals in the eighty-sixth week resulted in one litter (5 animals) and two failures. Eleven tests of Dose 1 animals from the eighty-third to the eighty-sixth week gave one positive (5 offspring) and 10 failures. This shows, at least, that some of these animals were not sterile.

Effects on Weight of Testis at Autopsy: The weight of the testis was not reduced by Doses 1 and 2 (especially when body weight was considered), but in Dose 3 mice it was slightly less than the control value. Dose 4 irradiation greatly reduced the testis weight. These results are shown in Figure 19.

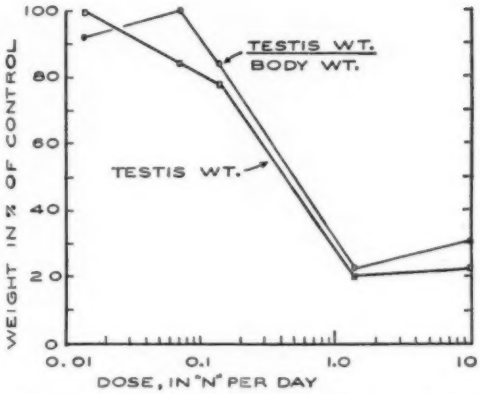

Fig. 19. The mean weight of the testis, and that relative to the entire body weight, plotted against the daily dose of neutrons.

TABLE XIV: HYPOPLASIA OF TESTIS, SPERMATOGENESIS

Animals	Controls	Dose 1, 0.014 "N" per Day	Dose 2, 0.07 "N" per Day	Dose 3, 0.14 "N" per Day	Dose 4, 1.4 "N" per Day
No. examined	32	34	30	37	33
Per cent uninjured	78	85	73.5	38	0
Per cent control	100	109	94	49	0
Per cent injured	0	0	6	51	100

Histologic Study of the Testis: All of the Dose 4 testes showed aspermia and aspermatogenesis. Only sertoli cells and an occasional spermatogonium remained in the tubules. Testes of Dose 3 animals usually showed aspermia but earlier stages of spermatogenesis were present. Activity was reduced and injured cells were in evidence. Testes of Dose 2, Dose 1, and control animals were uninjured except in the presence of heavy infection, etc. A few testes of the Dose 2 group appeared to have slightly reduced spermatogenic activity. The results are summarized in Table XIV.

Relative Effect of Different Doses of Neutrons on Various Organs: A complete histologic analysis was impossible, as many of the tissues (especially the intestine) had undergone some postmortem autolysis. From 26 to 37 animals in each group were sacrificed or were preserved soon enough after death to permit at least a tentative estimate of the degree of hypoplasia produced.

The frequency of injury in percentage of controls was calculated in the same way as for Table XIV and the results are summarized in Figure 20. One week after an exposure of 70 to 90 "N," the organs most definitely affected were the spleen, bone marrow, and intestine. A month after a single dose of 60–80 "N," the gonads exhibited the most frequent signs of hypoplasia. The bone marrow and liver were still injured, but the spleen and intestine had apparently recovered to some extent

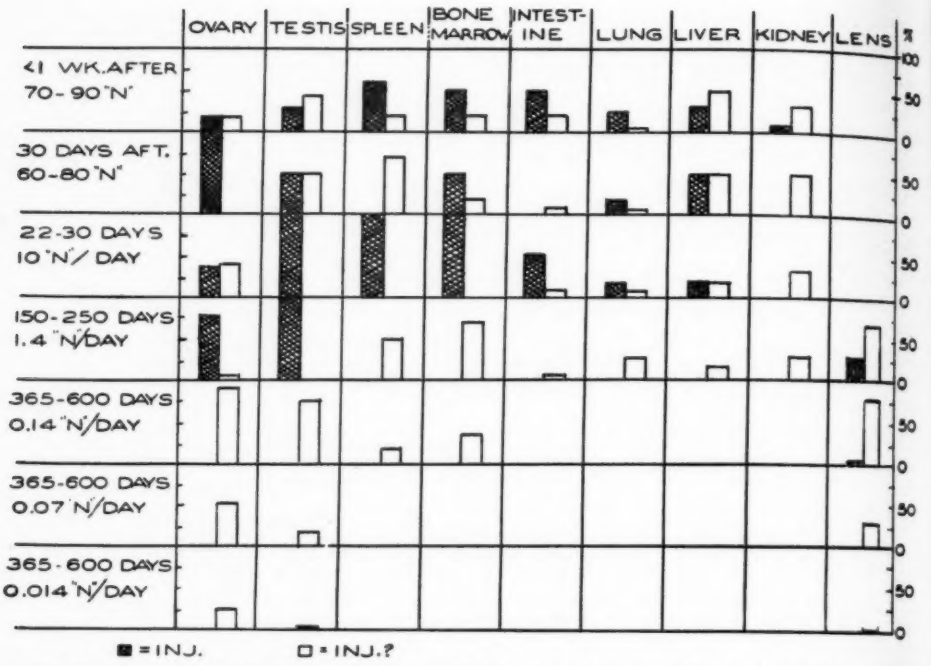

Fig. 20. Chart showing the relative occurrence of injury in various organs following irradiation. In the upper row of graphs are shown the effects of a single exposure from 70 to 90 "N," about a week after the irradiation. The effects after a single exposure of from 60 to 80 "N" are shown in the second row from the top. These effects were at about thirty days after irradiation. The results shown in the third row from the top followed 22 to 30 days of daily exposures of 10 "N." The animals of the four lower rows received small daily doses as indicated and were examined near the end of the experiment.

in the month's time. Testes, spleen, and marrow examined after twenty-two to thirty days of exposure to 10 "N" per day showed, universally, extreme hypoplasia. The ovaries and intestines of such animals also were injured, but to a lesser degree.

Gonads of animals receiving 1.4 "N" per day, and examined between the 150th and 250th day, showed hypoplasia to a marked extent. The spleen and bone marrow usually were slightly hypoplastic. All of the eyes at this time had well developed cataracts, and about one-fourth of the animals were evidently blind. Cataracts were not seen in the animals of the previously described experiments, apparently because the time after radiation exposure was too short. Two animals exposed to a single dose of 70 "N" survived for about a year and each had extensive cataracts in both eyes.

After a year to six hundred days of 0.14 "N" per day exposures, there was no indication of severe injury. The gonads, especially the ovaries, frequently showed some indications of hypoplasia, but it was not always possible to rule out such factors as senility, disease, and postmortem autolysis. Such condition also occasionally appeared in the bone marrow and spleen. The frequency of cataract was high, but the condition was not pronounced and could be seen only by examining with the slit lamp and binocular dissecting microscope.

As shown in Figure 20, the only indications of histologic damage produced by the two lowest daily doses used were hypoplasia of the gonads and cataracts. Whether these changes indicated radiation damage is questionable.

The occurrence of neoplasia is indicated in Table XV. The frequency was high

even in the controls. This value was due primarily to lung tumors, which were present in about half of the animals examined near the end of the experiment. These tumors apparently developed late in life and occurred usually in lobes showing evidence of earlier infection and inflammation. The radiation exposures did not increase the frequency of neoplasms except possibly in the case of leukemoid hyperplasia of Dose 3 animals. Of the 12 cases in the Dose 3 group, 8 occurred during the first year. In three other groups (Controls, Dose 1, Dose 2), only 3 of 18 cases occurred during the first year of the experiment.

TABLE XV: OCCURRENCE OF NEOPLASIA

Condition	Controls	Dose 1, 0.014 "N" per Day	Dose 2, 0.07 "N" per Day	Dose 3, 0.14 "N" per Day	Dose 4, 1.4 "N" per Day
Number of instances					
Leukemoid hyperplasia	7	5	7	12	9
Lung neoplasm	23	23	27	29	4
Skin neoplasm	8	8	11	2	1
Liver neoplasm	2	1	0	2	1
Breast neoplasm*	1	4	0	1	0
Ovarian neoplasm*	2	3	1	2	0
Other neoplasms	2	3	1	2	0
Number of animals					
With two neoplasms	4	4	5	4	0
With one neoplasm	37	36	36	42	15
With no neoplasm	57	54	47	48	82

* These occurred only in females, which group represented about half of the total number of animals.

Effects of 1.4 "N" per Day Compared with Those of 11 r per day: The production of cataracts, the early cessation of estrous cycles, and injury to the testis were very noticeable effects of the 1.4 "N" per day irradiations. These criteria were not employed in the preliminary experiments to determine the r/"N" ratio for "acute" (single exposure) and "subacute" fractionated (10 "N"/day, 80 r/day) treatments. The question then arose as to whether the ratio (8 r = 1 "N") for "chronic" irradiation would be different from that for the other two methods of exposure. Another possibility was that the lens and gonads were especially sensitive to neutrons. Therefore, three additional experiments were done to compare several effects of 1.4 "N"/day with those of 11 r/day.

The results of the first experiment (Table XVI) indicated that 1.4 "N"/day was more effective than 11 r/day in producing cataracts, reducing survival time, decreasing body weight, producing sterility, reducing weight of testis, and reducing weight of spleen. On the other hand, 11 r/day was more effective in lowering the percentage of lymphocytes, the hemoglobin, and leukocyte count.

In the second experiment (Table XVII), the effects of 1.4 "N"/day were found to be greater for production of cataracts, for reduction of survival time and body weight, and for production of anestrus. The effects of the two kinds of irradiation were about the same as regards injury to the blood and reduction of spleen weight.

At the time 50 per cent of the irradiated animals had died the total dose that had been administered was 12 times greater for x-rays than for neutrons (Table XVII and XVIII). This does not mean, necessarily, that a dose of 12–13 r/day would be required to kill the animals at the same time as would 1 "N"/day. It does indicate, however, a strong probability that the ratio of r/day to "N"/day for chronic exposures is at least slightly higher than 11 r/day = 1.4 "N"/day. It is also indicated that the ratio of r to "N" for chronic exposures is much higher for such effects as production of cataract and injury to reproductive organs than for the others studied.

DISCUSSION

The problem of determining a daily acceptable exposure for neutron radiation has been discussed in a recent symposium on the Plutonium Project by Zirkle *et al.* (7). The report of Henshaw, Riley, and Stapleton (8) is especially pertinent to the present discussion. These investigators obtained a ratio of 1 n = 7.5–8 r for acute killing of mice. Although it is purely a coincidence (as we used a different source, different measuring instrument, and different strains of animals), our value is prac-

TABLE XVI: COMPARISON OF EFFECTS OF X-RAYS AND NEUTRONS
(25 Swiss Males in Each Group)

	1.4 "N"/Day 7 "N"/Wk.	11 r/Day 55 r/Wk.	Greater Effect with
Lethal time 50, in days	183	275	1.4 "N"/day
Total dose at L.T. 50	175 "N"	2,112 r	1.4 "N"/day
Body weight at L.T. 50, % controls	68	87	1.4 "N"/day
Weeks fertile	5	23–31	1.4 "N"/day*
Dose for sterility	25 "N"	1,155–1,577 r	1.4 "N"/day*
Testis wt./body wt., % control	30	69	1.4 "N"/day
Spleen wt./body wt., % control	86	100	1.4 "N"/day
No. eyes with pronounced cataract in animals surviving after L.T. 50, % controls	55	8?	1.4 "N"/day
R.B.C. at L.T. 50, % control	60	77	1.4 "N"/day ?
Per cent lymphocytes at L.T. 50, % controls	69	62	11 r/day ?
Hemoglobin at L.T. 50, % controls	82	68	11 r/day
W.B.C. at L.T. 50, % Controls	63	37	11 r/day

* Much greater.

TABLE XVII: COMPARISON OF EFFECTS OF X-RAYS AND NEUTRONS
(17 Swiss Females in Each Group)

	1.4 "N"/Day 7 "N"/Wk.	11 r/Day 55 r/Wk.	Greater Effect with
L.T. 50, in days	175	263	1.4 "N"/day !
L.D. 50	158 "N"	2,112 r	1.4 "N"/day !
Body wt. at L.T. 50, % controls	77	96	1.4 "N"/day
Body wt., % controls at autopsy	58	65	...
Spleen wt./body wt., % controls	106	56	11 r/day
Spleen wt., % controls	62	55.7	...
Time to produce anestrus (weeks)	18	32	1.4 "N"/day !
Dose to produce anestrus	126 "N"	1,760	1.4 "N"/day !
No. eyes with cataract in animals surviving after L.T. 50, % controls	50	0	1.4 "N"/day !
Blood, % controls, at L.T. 50, for neutrons:			
% lymphocytes	73	87	1.4 "N"/day ?
W.B.C.	36	39	?
R.B.C.	95	99	?
Hemoglobin	105	95	?
Blood, % controls, at L.T. 50, for x-rays:			
% lymphocytes	43	69	1.4 "N"/day
Hemoglobin	82	83	?
R.B.C.	86	75	11 r/day ?
W.B.C.	66	32	11 r/day

TABLE XVIII: COMPARISON OF EFFECTS OF X-RAYS AND NEUTRONS
(25 Swiss Males in Each Group)

	1.4 N/Day 7 N/Wk.	11 r/Day 55 r/Wk.	15 r/Day 75 r/Wk.	Greater Effect with
Weeks for complete sterility	8	16	12	1.4 "N"/day‡
Dose for complete sterility	56*	825*	900*	1.4 "N"/day‡
	45†	990†	1,050†	1.4 "N"/day‡
Body wt., % controls	86	100	96	1.4 "N"/day ?
Testis wt./body wt., % controls	55	59	60	1.4 "N"/day ?
Weeks for aspermatogenesis	10–11	15	11	1.4 "N"/day ?
Weeks after irradiation for some recovery of spermatogenesis	2+	2	2	1.4 "N"/day
Spleen wt./body wt., % controls	68	68	53	15 r/day
Blood, % controls, 15th, 16th, and 17th weeks				
Hemoglobin	82	89	96	?
R.B.C.	82	84	87	?
% lymphocytes	55	67	48	15 r/day
W.B.C.	49	67	35	15 r/day

* Planned dose based on 5 treatments per week.
† Actual dose given.
‡ Much greater.

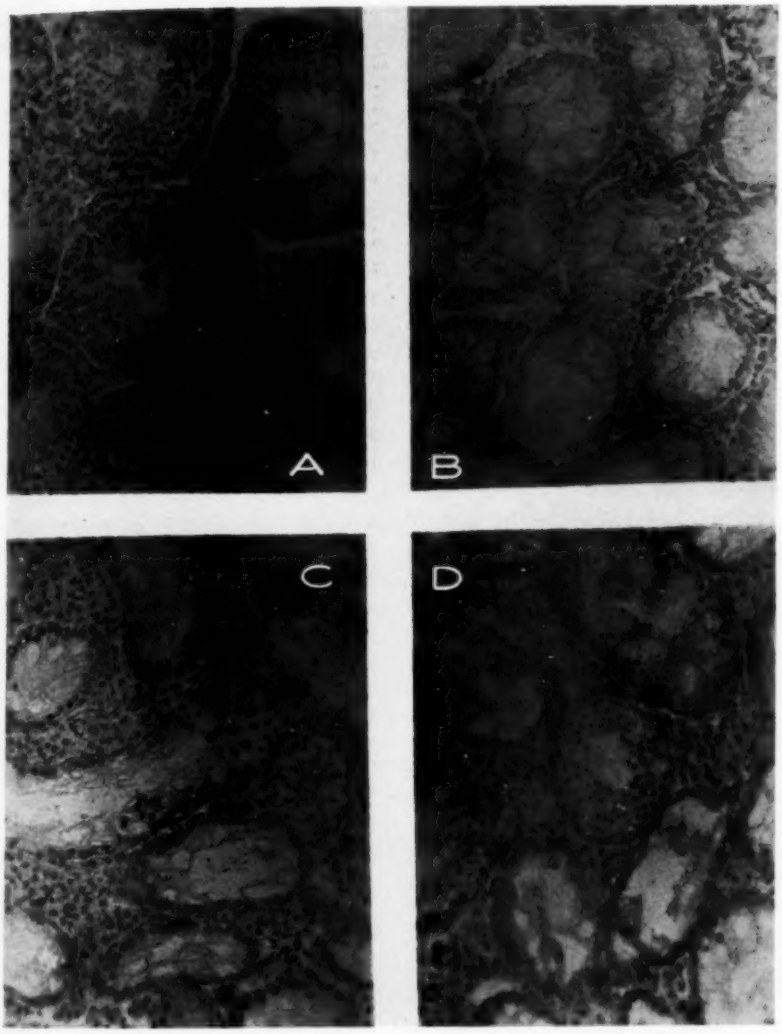

Fig. 21. Photomicrographs (×150) of representative regions of the testes of animals two weeks after the conclusion of the irradiation period (15 weeks).

A. Control testis. Note active spermatogenesis.

B. Testis of animal receiving 1.4 "N" per day. Germinal epithelium does not appear to be injured to the degree that it was a few weeks previously, but spermatogenic activity has not been resumed.

C. Testis of animal receiving 15 r per day. Early stages of spermatogenesis are evident in three tubules. Apparently the germinal epithelium has begun to recover activity.

D. Testis of animal exposed to 11 r per day. Recovery of spermatogenic activity has progressed to a greater extent than in B or C, although some tubules in this section have remained inactive.

tically identical with theirs. Our other findings which are in general agreement with those of the above authors are: (1) the r/"N" ratio is higher for smaller daily doses than for acute irradiations; (2) reduction of survival time was one of the most sensitive responses; (3) the lowest daily dose which produced a definite reduction in survival time was in the neighborhood of 0.1 "N"; (4) in general, the peripheral blood did not change much with daily doses in the range of 0.1 "N."

It appears that the r/"N" ratio we obtained for small daily doses is lower than that found by Henshaw *et al.* (8). These authors obtained a value of 1 n = 35 r. This was done by placing the point representing the percentage shortening of life by 8.6 r/day of gamma rays on a curve which showed the percentage shortening of life by different daily doses of neutrons. The effect of 8.6 r/day then corresponded to that of 0.25 n/day. The method used to obtain the r/n ratio for acute death was based on the doses required to kill 50 per cent of the animals within a certain short period of time. The data of the above authors would indicate 2,400 r = 200 n (or approx. 12 r = 1 n) if one compares the total dose delivered at L.T. 50 (of original number) of 8.6 r/day with that of 1.15 n/day. (This assumes that survival curves of the two lots of controls are the same.) The figures we obtained by comparing the total dose at L.T. 50 in two different experiments (Tables XVI and XVII) were 12.2–13.5 r = 1 "N." If the percentage reduction of survival time is used (as employed by Henshaw *et al.*) on our data, it is found that 11 r/day reduced the L.T. 50 by 40 per cent and 1.4 "N"/day reduced it by 55 per cent. By interpolation (Fig. 9) we would expect a 40 per cent reduction to be produced by 0.62 "N" per day. Thus, 0.62 "N" = 11 r and 1 "N" = 18 r.

Although the value for the r/"N" ratio appears to vary with conditions and methods used, it does seem to be higher for small daily doses than for the acute exposures. The basis for this difference may be that x-rays and gamma rays are more selectively injurious to mitotically active cells, whereas neutron radiation injures active and inactive cells more similarly. Evidence for this has been obtained on other materials (Marshak 9, 10; Gray, 11; Spear, 12). It might be expected that each additional daily dose of neutrons would exert a relatively greater cumulative effect in our animals than would be obtained with x-rays if this difference in action took place.

It also appears that the r to "N" ratio (for small daily doses) may vary from one tissue to another. The effect of 1.4 "N"/day on cataract formation was so much more pronounced than that of 11 r/day that an evaluation of the r/"N" ratio for this effect could not be estimated. The ratio of r to "N" for the total dose administered at the time mating tests (of males) became negative was 46 in one experiment and 22 in the other. There was, of course, considerable variation in the value in the two experiments, as this method of estimating degree of injury is very rough. However, it does appear that the r to "N" ratio for daily doses, in the range employed, was appreciably higher than that based on reduction of survival time.

It should be emphasized that although some effects (such as blood changes) did not appear to increase in severity as the 0.1 "N"/day irradiation progressed, others did. Eventually, the number of survivors was reduced to less than 50 per cent of the control value. In addition, the total dose administered at this time was only 60 "N," whereas about 200 "N" had been given at L.T. 50 in the 1.4 "N"/day experiments. Thus it seems that a lower daily dose may be more effective per "N," although it requires much more time. This has been indicated previously for x-radiation (Henshaw, 6).

It is beyond the scope of the present paper to attempt to relate these findings to the problem of establishing a daily acceptable neutron dose for man. It is well to emphasize, however, that when such a problem is considered, the indication of delayed effects of small daily doses being greater for neutrons than for x-rays should be taken into account.

CONCLUSIONS

Daily doses of 0.014 "N" of fast neutrons (0.07 "N"/wk.), equivalent to 0.1 r/day of x-rays (on the basis of relative effects of single exposures), had no definite effect on mice treated for approximately eighty-seven weeks.

Some effects (though still not pronounced) were observed in animals exposed

daily to 0.07 "N," with a total dose of approximately 30 "N."

Daily exposures of 0.14 "N" (total of 60 "N") definitely reduced survival time slightly, reduced growth activity of hemopoietic organs and gonads, and slightly increased the frequency of cataracts.

Doses of 1.4 "N" per day resulted in death of over 50 per cent of the animals by about the twenty-ninth week (total "N" = approximately 200). This irradiation caused pronounced changes within a few weeks in blood counts, activity of hemopoietic organs and gonads. In addition, extreme damage to the lens was evident by the time half of the original number of animals had died.

Daily exposures of 1.4 "N" were more effective than those of 11 r (equivalents on the basis of relative effects of single exposures). Some effects, based on total dose at time of appearance, indicated a ratio of 12–13 r = 1 "N." The effects of 1.4 "N" per day on gonads and lens were more pronounced than even this ratio, 12 r = 1 "N," would indicate.

Considering the results generally, the most important finding was that the lens was especially sensitive to the neutron radiation.

NOTE: The writer wishes to express his appreciation to Dr. G. Failla for his constructive criticisms throughout the investigation. It is also a pleasure to acknowledge the assistance of the following: Mr. Walter Wilson, Miss Grace Clarke, Miss Anne Behan, Miss Gertrude Lange, Mr. Edgar Werner, Miss Lorna Pitz, and Mr. John Anthony.

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SUMARIO

Efectos de las Pequeñas Dosis Diarias de Neutrones Veloces sobre los Ratones

El estudio actual comprendió los efectos de los neutrones veloces, producidos por el ciclotrón de 90 cm. de los Laboratorios Pupin de la Universidad de Columbia, sobre ratones de ambos sexos y de dos razas distintas. Como medida de la dosis se tomó una unidad arbitraria, "N," basada en la yonización producida en una cámara Victoreen de 25 r. (La unidad n, que utilizan otros técnicos, se basa generalmente en la yonización en una cámara Victoreen de 100 r.) Las siguientes son las observaciones realizadas.

Dosis diarias de 0.014 "N" de neutrones veloces (0.07 "N" semanales), equivalentes á 0.1 r diario de rayos X (a base de los efectos relativos de una sola exposición), no ejercieron efecto preciso sobre los ratones tratados por unas 87 semanas.

En los animales expuestos diariamente a 0.07 "N," con una dosis total de unas 30 "N," se observaron ciertos efectos (pero tampoco pronunciados).

La exposiciones diarias a 0.14 "N" (con un total de 60 "N") rebajaron ligeramente el tiempo de sobrevivencia, mermaron el

desarrollo activo de los órganos hematopoyéticos y los gonados y acrecentaron ligeramente la frecuencia de las cataratas.

Las dosis diarias de 1.4 "N" produjeron la muerte de más de 50 por ciento de los animales para la vigésimanovena semana (total de "N" = approximadamente 200). Esta irradiación ocasionó profundas alteraciones en pocas semanas en la hematimetría, actividad hematopoyética y gonados. Además, para la fecha en que habia muerto la mitad del primitivo número de animales había signos de intensas lesiones del cristalino.

Las exposiciones diarias a 1.4 "N" resultaron más efectivas que las de 11 r (equivalentes a base de los efectos relativos de exposiciones aisladas). Algunos efectos indicaban, a base de la dosis total en la fecha de su aparición, una razón de 12-13 r = 1 "N." Los efectos de 1.4 "N" al día sobre los gonados y el cristalino fueron aun más pronunciados que lo que indicaría dicha razón de 12 r = 1 "N."

Considerando el resultado en general, el hallazgo más importante fué que el cristalino era en particular susceptible a la irradiación con neutrones.

No se trató de correlacionar estos hallazgos con el problema de establecer una dosis diaria aceptable de neutrones para el hombre. Sin embargo, conviene recalcar que, al considerar dicho problema, hay que tomar en cuenta la indicación de que los efectos tardíos de las pequeñas dosis diarias son mayores para los neutrones que para los rayos X.

EDITORIAL

Streptomycin in Tuberculosis

In spite of a tremendous volume of careful work which has contributed largely to our knowledge of the nature of tuberculosis and to elaboration of a treatment regimen that has been productive of great good, the disease has remained persistently resistant to attack. No specific and no cure has yet stood the test of time, although hundreds have been offered. Of these, only one has shown the capacity to influence the disease in man—streptomycin.

In January 1944, Schatz, Bugie, and Waksman (1) presented "a new antibacterial substance, designated as streptomycin." This occasioned little general notice until it was shown, in November of that year (2), that the new antibiotic inhibited the growth of *M. tuberculosis*. Shortly thereafter Feldman and Hinshaw applied the drug to tuberculous guinea-pigs with favorable results and were able to report its salutary effects on certain types of tuberculosis in human beings (3).

These epoch-making observations were followed by intensive experimental and clinical studies and now, for the first time in the history of medicine, a drug is available that exerts a distinctly favorable influence upon tuberculosis in man. Careful clinical observations have been made by various workers, but the drug has been scarce. A few individual investigators, the Veterans Administration and the Army and Navy (4), the United States Public Health Service (5), and the Therapy Committee of the American Trudeau Society (6) have, altogether, studied the effects of the drug in about 2,000 patients, with results which suggest the following deductions:

(1) Streptomycin should be tried in all cases of miliary tuberculosis, for more than half of such patients will be alive, and a substantial number of them will be free from clinical, x-ray, or laboratory signs of disease, six to twelve months after discontinuation of the drug.

(2) The use of the drug in tuberculous meningitis is mandatory, for about one-fourth of all patients have survived from six to twelve months after treatment, and the majority of these are free from detectable signs of tuberculosis.

(3) Acute tuberculous pneumonia or exudative (fresh) tuberculous disease of the lungs will usually show recession, with notable clearing of the lungs demonstrable roentgenographically within a few weeks. Tubercle bacilli disappear from the sputum in about half these cases. Such patients however, need still further sanatorium care.

(4) Extrapulmonary tuberculosis is under detailed study, but already it appears that tuberculous laryngitis and bronchitis are benefited by the use of streptomycin in about 85 per cent of cases, even though the parent lesion in the lungs may show no improvement. Tuberculous enteritis and cystitis likewise tend to improve. In fact, in areas in which the disease affects the epithelial surfaces, results are generally good. Cutaneous sinuses do well. Tuberculosis of the osseous and genito-urinary systems needs further study.

(5) Streptomycin is used profitably at times to enhance the patient's chances from collapse therapy and as a prophylactic in surgical treatment, particularly pulmonary resection.

The disturbing fact, in the face of these relatively good results, is this—that the average case of fibrocavernous tuberculosis has been found as yet to respond poorly to streptomycin, and this type represents three-fourths of all cases of the disease. It

is still under intensive study. Two other disquieting factors are the toxicity of the drug and the development of streptomycin-fastness by the tubercle bacillus.

In the early experience with this drug, with large doses, of 2, 3, or even 5 grams a day, toxic symptoms were very common. Even with a standard dose of 1.8 gm., vertigo developed in approximately 92 per cent of one large series of patients. McDermott (7), among others, has pointed out the common indices of toxicity. Vestibular dysfunction predominates, characterized by vertigo, dizziness, headache, and nausea, some of which are present to some degree in almost all patients who take large doses. Vertigo occurs in 20 per cent or more of those receiving 1.0 gm. per day, which is now the prevailing dose. It may be permanent. Deafness, partial or complete, has been observed. It occurs rarely except when the drug is applied intrathecally for tuberculous meningitis or (less often) in persons with impaired renal function who receive large doses. Further damage to the kidneys may occur in this latter group, which indicates the propriety of determining the condition of the urinary tract prior to administration of the drug. In patients with already lowered renal function, blood levels may become high and various toxic symptoms ensue. Other indications of toxicity are anaphylactic manifestations—fever, itching, dermatitis and eosinophilia—and agranulocytosis. The latter appears in less than 1 per cent of cases and is usually an indication for prompt discontinuation of treatment.

The development of streptomycin resistance by the tubercle bacillus (8), occurring rather regularly, presents a serious obstacle in the use of the drug. Whether this represents biological adjustment to a new environment or the survival and increasing preponderance of natively resistant bacilli in the diseased body is not known. Once it becomes manifest, however, it appears to persist, and resistant strains have been maintained in culture for considerably over a year and have been passed through animals without reverting (9).

The production of resistant strains should be a serious consideration in the therapeutic use of streptomycin in patients palpably unlikely to recover, for the spread of such strains could conceivably become a grave public health hazard. To obviate this, careful selection of cases and frequent *in vitro* examination after the first six weeks of treatment are indicated, while continuation of the drug beyond six weeks is to be discouraged.

In general, streptomycin should be withheld in cases of minimal tuberculosis and in those in which conventional treatment offers reasonable prospect of good result. It provides an excellent medium of treatment for certain types of tuberculosis, but it should be used in association with accepted therapeutic measures and not as a substitute for them. As a matter of fact, a healthy tendency is at present developing to use the drug only as an adjunct rather than as a definitive treatment in all types of tuberculosis except the miliary and meningitic forms, to apply it briefly for three, four, or six weeks, at the most opportune time, with other appropriate therapy.

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Invitation to San Francisco

Seven eventful years have passed since the Radiological Society last met in San Francisco, seven years which saw many of its members pass through that city bound for radiological duty with the military forces in various parts of the world. It is therefore with pride and pleasure that we again invite all radiologists, but especially the members of the Radiological Society of North America, to attend the annual meeting to be held in San Francisco Dec. 5 to 10, 1948.

San Francisco, the city, and San Francisco, the medical center, is prepared to extend its facilities to members and guests. As a medical center the term "Bay Area" would be more appropriate, since we really mean the radiologists and other physicians of San Francisco, Alameda, and the adjoining counties, the California Medical Association, the medical schools, and the scientific institutions of the Bay Area.

THE SETTING

In addition to its attraction as the medical center of the Pacific Coast, San Francisco is known to many of you for its beauty and surroundings. It is approached from the south by El Camino Real, the old highway of the padres, from the east and north by the two famous Bay bridges, and from the west by the rolling Pacific. The redwoods in Muir Park, in Marin County, are well worth a visit. The fabled Valley of the Moon and the historic Spanish missions may be reached by short automobile drives. You may leave San Francisco by morning and dine the same evening in the Hawaiian Islands, returning to the mainland for supper on the following day. You may fly to Reno and be skiing on Mount Rose in two hours time. So plan to come with opportunities to indulge in more than intellectual pursuits.

THE SCIENTIFIC PROGRAM

An unusually stimulating program has been arranged. It will consist of a series of symposia, of groups of related papers, of scientific exhibits, and refresher courses. The symposia will include the following: "A Wet Clinic on the Practical Use of Isotopes," by Dr. W. E. Chamberlain, Dr. Earl Miller, and associates; "Practical Biopsy Procedures and Evaluation of Cytological Methods," by Drs. Budd, Farber, and associates. "A Practical Approach to the Roentgen Diagnosis of Congenital Cardiovascular Lesions," by Dr. Leo Rigler and associates. Dr. Shimkin and Dr. VanWinkle will bring us up to date on chemotherapy and hormonal treatment of cancer. Dr. Stone is arranging a special symposium on the chemical effects of irradiation, with some distinguished chemists and biologists taking part. There will be panels on "Permissible Total Body Irradiation, Relative to Atomic Explosion," "Diagnosis of Healing in Peptic Ulcer," and other topics.

The refresher courses in diagnosis and therapy have been revised and expanded, and members are advised to register early for those courses which they wish to take. Dr. Merrill Sosman will give the Carman Lecture and, as might be expected, has chosen a most interesting topic. There will be afternoons devoted to improved methods for the diagnosis of intracranial lesions, practical aspects of pediatric roentgenology, etc. The scientific exhibits promise to be of considerable merit. Many will be "tied in" with the symposia and panel discussions, making these sessions of even greater value than usual.

THE INSTITUTES

Besides the scientific programs, there will be many things to interest you while in San Francisco. The various cyclotrons at the State University at Berkeley, together with the departments of medical physics and medical research at that center; the laboratory of Experimental Oncology at the Laguna Honda Home in San Francisco (a joint project of the National Cancer Institute, the U. S. Public Health Service and the local medical schools); the Isotope Laboratory at the University of California Medical School Hospital in San Francisco, and at Letterman General Hospital (the only one at an Army Hospital in the United States).

ENVOI

Plan now to attend the December meeting. San Francisco and the Pacific Coast will uphold their reputation for hospitality, and the papers and exhibits will make your visit well worth while.

L. HENRY GARLAND, M.D.
President

RADIOLOGICAL SOCIETIES: SECRETARIES AND MEETING DATES

Editor's Note: Secretaries of state and local radiological societies are requested to co-operate in keeping this section up-to-date by notifying the editor promptly of changes in officers and meeting dates.

UNITED STATES

RADIOLOGICAL SOCIETY OF NORTH AMERICA. *Secretary-Treasurer*, Donald S. Childs, M.D., 607 Medical Arts Bldg., Syracuse 2, N. Y.

AMERICAN RADIUM SOCIETY. *Secretary*, Hugh F. Hare, M.D., 605 Commonwealth Ave., Boston 15, Mass.

AMERICAN ROENTGEN RAY SOCIETY. *Secretary*, Harold Dabney Kerr, M.D., Iowa City, Iowa.

AMERICAN COLLEGE OF RADIOLOGY. *Secretary*, Mac F. Cahal, 20 N. Wacker Dr., Chicago 6, Ill.

SECTION ON RADIOLOGY, A. M. A. *Secretary*, U. V. Portmann, M.D., Cleveland Clinic, Cleveland 6, Ohio.

Alabama

ALABAMA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Courtney S. Stickley, M.D., Bell Bldg., Montgomery. Next meeting with State Medical Association.

Arkansas

ARKANSAS RADIOLOGICAL SOCIETY. *Secretary*, Fred Hames, M.D., Pine Bluff. Meets every three months and at meeting of State Medical Society.

California

CALIFORNIA MEDICAL ASSOCIATION, SECTION ON RADIOLOGY. *Secretary*, Sydney F. Thomas, M.D., Palo Alto Clinic, Palo Alto.

LOS ANGELES RADIOLOGICAL SOCIETY. *Secretary*, Moris Horwitz, M.D., 2009 Wilshire Blvd., Los Angeles 5. Meets second Wednesday of each month at County Society Bldg.

PACIFIC ROENTGEN SOCIETY. *Secretary*, L. Henry Garland, M.D., 450 Sutter St., San Francisco 8. Meets annually with State Medical Association.

SAN DIEGO ROENTGEN SOCIETY. *Secretary*, R. F. Niehaus, M.D., 1831 Fourth Ave., San Diego. Meets first Wednesday of each month.

X-RAY STUDY CLUB OF SAN FRANCISCO. *Secretary*, Ivan J. Miller, M.D., 2000 Van Ness Ave. Meets monthly on the third Thursday at 7:45 P.M., January to June at Lane Hall, Stanford University Hospital, and July to December at Toland Hall, University of California Hospital.

Colorado

DENVER RADIOLOGICAL CLUB. *Secretary*, Mark S. Donovan, M.D., 306 Majestic Bldg., Denver 2. Meets third Friday of each month, at the Colorado School of Medicine and Hospitals.

Connecticut

CONNECTICUT STATE MEDICAL SOCIETY, SECTION ON RADIOLOGY. *Secretary*, Robert M. Lowman, M.D., Grace-New Haven Hospital, Grace Unit, New Haven. Meetings bimonthly, second Thursday.

District of Columbia

RADIOLOGICAL SECTION, DISTRICT OF COLUMBIA MEDICAL SOCIETY. *Secretary*, Alfred A. J. Den, M.D., 1801 K St., N. W., Washington 6. Meets third Thursday of January, March, May, and October, at 8:00 P.M., in Medical Society Auditorium.

Florida

FLORIDA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, J. A. Beals, M.D., St. Luke's Hospital, Jacksonville. Meets in April, preceding annual meeting of Florida Medical Society, and in November.

Georgia

GEORGIA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Robert Drane, M.D., De Renne Apartments, Savannah. Meets in November and at the annual meeting of State Medical Association.

Illinois

CHICAGO ROENTGEN SOCIETY. *Secretary*, T. J. Wachowski, M.D., 310 Ellis Ave., Wheaton. Meets at the Palmer House, second Thursday of October, November, January, February, March, and April, at 8:00 P.M.

ILLINOIS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, William DeHollander, M.D., St. Johns' Hospital, Springfield. Meetings quarterly as announced.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON RADIOLOGY. *Secretary*, John H. Gilmore, M.D., 720 N. Michigan Ave., Chicago 11.

Indiana

INDIANA ROENTGEN SOCIETY. *Secretary-Treasurer*, J. A. Campbell, M.D., Indiana University Hospitals, Indianapolis 7. Annual meeting in May.

Iowa

IOWA X-RAY CLUB. *Secretary*, Arthur W. Erskine, M.D., 326 Higley Building, Cedar Rapids. Meets during annual session of State Medical Society.

Kentucky

KENTUCKY RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Sydney E. Johnson, M.D., 101 W. Chestnut St., Louisville.

LOUISVILLE RADIOLOGICAL SOCIETY, *Secretary-Treasurer*, Everett L. Pirkey, Louisville General Hospital, Louisville 2. Meets second Friday of each month at Louisville General Hospital.

Louisiana

LOUISIANA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Johnson R. Anderson, M.D., No. Louisiana Sanitarium, Shreveport. Meets with State Medical Society.

ORLEANS PARISH RADIOLOGICAL SOCIETY. *Secretary*, Joseph V. Schlosser, M.D., Charity Hospital of Louisiana, New Orleans 13. Meets first Tuesday of each month.

SHREVEPORT RADIOLOGICAL CLUB. *Secretary*, Oscar O. Jones, M.D., 2622 Greenwood Road. Meets monthly September to May, third Wednesday.

Maryland

BALTIMORE CITY MEDICAL SOCIETY, RADIOLOGICAL SECTION. *Secretary*, Harry A. Miller, 2452 Eutaw Place, Baltimore.

Michigan

DETROIT X-RAY AND RADIUM SOCIETY. *Secretary-Treasurer*, E. R. Witwer, M.D., Harper Hospital, Detroit 1. Meetings first Thursday of each month from October to May, at Wayne County Medical Society club rooms.

MICHIGAN ASSOCIATION OF ROENTGENOLOGISTS. *Secretary-Treasurer*, R. B. MacDuff, M.D., 220 Genesee Bank Building, Flint 3.

Minnesota

MINNESOTA RADIOLOGICAL SOCIETY. *Secretary*, C. N. Borman, M.D., 802 Medical Arts Bldg., Minneapolis 2. Regular meetings in the Spring and Fall.

Missouri

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY. *Secretary*, Wm. M. Kitchen, M.D., 1010 Rialto Building, Kansas City, 6, Mo. Meetings last Friday of each month.

ST. LOUIS SOCIETY OF RADIOLOGISTS. *Secretary*, Edwin C. Ernst, M.D., 100 Beaumont Medical Bldg. Meets on fourth Wednesday, October to May.

Nebraska

NEBRASKA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Ralph C. Moore, M.D., Nebraska Methodist Hospital, Omaha 3. Meetings third Wednesday of each month at 6 P.M. in either Omaha or Lincoln.

New England

NEW ENGLAND ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, George Levene, M.D., Massachusetts Memorial Hospitals, Boston. Meets monthly on third Friday at Boston Medical Library.

New Hampshire

NEW HAMPSHIRE ROENTGEN SOCIETY. *Secretary-Treasurer*, Albert C. Johnston, M.D., Elliot Community Hospital, Keene. Meetings quarterly in Concord.

New Jersey

RADIOLOGICAL SOCIETY OF NEW JERSEY. *Secretary*, Raphael Pomeranz, M.D., 31 Lincoln Park, Newark 2. Meetings at Atlantic City at time of State Medical Society and midwinter in Newark as called.

New York

ASSOCIATED RADIOLOGISTS OF NEW YORK, INC. *Secretary*, William J. Francis, M.D., East Rockaway, L. I.

BROOKLYN ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, Abraham H. Levy, M.D., 1354 Carroll St., Bklyn. 13. Meets fourth Tuesday of every month, October to April.

BUFFALO RADIOLOGICAL SOCIETY. *Secretary-Treasurer*. Mario C. Gian, M.D., 610 Niagara St., Buffalo 1. Meetings second Monday evening each month, October to May, inclusive.

CENTRAL NEW YORK ROENTGEN SOCIETY. *Secretary-Treasurer*, Dwight V. Needham, M.D., 608 E. Genesee St., Syracuse 10. Meetings in January, May, and October.

LONG ISLAND RADIOLOGICAL SOCIETY. *Secretary*, Marcus Wiener, M.D., 1430 48th St., Brooklyn 19. Meetings fourth Thursday evening, October to May, at 8:45 P.M., in Kings County Medical Bldg.

NEW YORK ROENTGEN SOCIETY. *Secretary*, Wm. Snow, M.D., 941 Park Ave., New York 28.

QUEENS ROENTGEN RAY SOCIETY. *Secretary*, Jacob E. Goldstein, M.D., 88-29 163rd St., Jamaica 3. Meets fourth Monday of each month.

ROCHESTER ROENTGEN-RAY SOCIETY. *Secretary*, Murray P. George, M.D., 260 Crittenden Blvd., Rochester 7. Meets at Strong Memorial Hospital, third Monday, September through May.

North Carolina

RADIOLOGICAL SOCIETY OF NORTH CAROLINA. *Secretary-Treasurer*, James E. Hemphill, M.D., Professional Bldg., Charlotte 2. Meets in May and October.

North Dakota

NORTH DAKOTA RADIOLOGICAL SOCIETY. *Secretary*, Charles Heilman, M.D., 1338 Second St., N., Fargo.

Ohio

OHIO STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Carroll Dundon, M.D., 2065 Adelbert Road, Cleveland 6. Next meeting at annual meeting of the State Medical Association.

CENTRAL OHIO RADIOLOGICAL SOCIETY. *Secretary*, Edward T. Kirkendall, M.D., 700 North Park St., Columbus 8.

CINCINNATI RADIOLOGICAL SOCIETY. *Secretary*, Eugene L. Saenger, M.D., 735 Doctors Bldg., Cincinnati 2. Meets last Monday, September to May.

CLEVELAND RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, George L. Sackett, M.D., 10515 Carnegie Ave., Cleveland 6. Meetings at 6:30 P.M. on fourth Monday, October to April, inclusive.

Oklahoma

OKLAHOMA STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Peter M. Russo, M.D., 230 Osler Building, Oklahoma City. Meetings three times a year.

Oregon

OREGON RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Wm. Y. Burton, M.D., 242 Medical Arts Bldg., Portland 5. Meets monthly, on the second Wednesday, at 8:00 P.M., in the library of the University of Oregon Medical School.

Pacific Northwest

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Sydney J. Hawley, M.D., 1320 Madison St., Seattle 4, Wash. Meets annually in May.

Pennsylvania

PENNSYLVANIA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, James M. Converse, M.D., 416 Pine St., Williamsport 8. Meets annually.

PHILADELPHIA ROENTGEN RAY SOCIETY. *Secretary*, Arthur Finkelstein, M.D., Graduate Hospital, Philadelphia. Meets first Thursday of each month at 8:00 P.M., from October to May in Thomson Hall, College of Physicians, 21 S. 22d St.

PITTSBURGH ROENTGEN SOCIETY. *Secretary-Treasurer*, R. P. Meader, M.D., 4002 Jenkins Arcade, Pittsburgh 22. Meets second Wednesday of each month at 6:30 P.M., October to June.

Rocky Mountain States

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Maurice D. Frazer, M.D., Lincoln Clinic, Lincoln, Nebr.

South Carolina

SOUTH CAROLINA X-RAY SOCIETY. *Secretary-Treasurer*, Robert B. Taft, M.D., 103 Rutledge Ave., Charleston 16.

Tennessee

MEMPHIS ROENTGEN CLUB. Meetings second Tuesday of each month at University Center.

TENNESSEE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, J. Marsh Frére, M.D., 707 Walnut St., Chattanooga. Meets annually with State Medical Society in April.

Texas

DALLAS-FORT WORTH ROENTGEN STUDY CLUB. *Secretary*, X. R. Hyde, M.D., Medical Arts Bldg., Fort Worth 2. Meetings on third Monday of each month in Dallas in the odd months and in Fort Worth in the even months.

HOUSTON X-RAY CLUB. *Secretary*, Curtis H. Burge, M.D., 3020 San Jacinto, Houston 4. Meetings fourth Monday of each month.

TEXAS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, R. P. O'Bannon, M.D., 650 Fifth Ave., Fort Worth 4. Next meeting Jan. 7–8, 1949.

Utah

UTAH STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, M. Lowry Allen, M.D., Judge Bldg., Salt Lake City 1. Meets third Wednesday, January, March, May, September, November.

UNIVERSITY OF UTAH RADIOLOGICAL CONFERENCE. *Secretary*, Henry H. Lerner, M.D. Meets first and third Thursdays, September to June, inclusive, at Salt Lake County General Hospital.

Virginia

VIRGINIA RADIOLOGICAL SOCIETY. *Secretary*, P. B. Parsons, M.D., Norfolk General Hospital, Norfolk 7.

Washington

WASHINGTON STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Homer V. Hartzell, M.D., 310 Stimson Bldg., Seattle 1. Meetings fourth Monday October through May, at College Club, Seattle.

Wisconsin

MILWAUKEE ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, A. Melamed, M.D., 425 E. Wisconsin Ave., Milwaukee 2. Meets monthly on second Monday at the University Club.

RADIOLOGICAL SECTION OF THE WISCONSIN STATE MEDICAL SOCIETY. *Secretary*, S. R. Beatty, M.D., 185 Hazel St., Oshkosh. Two-day meeting in May and one day with State Medical Society, September.

UNIVERSITY OF WISCONSIN RADIOLOGICAL CONFERENCE. Meets first and third Thursdays 4 P.M., September to May, Service Memorial Institute, Madison 6.

Puerto Rico

ASOCIACIÓN PUERTORRIQUEÑA DE RADIOLOGÍA.—*Secretary*, Jesus Rivera Otero, M.D., Box 3524, Santurce, Puerto Rico.

CANADA

CANADIAN ASSOCIATION OF RADIOLOGISTS. *Honorary Secretary-Treasurer*, E. M. Crawford, M.D., 2100 Marlowe Ave., Montreal 28, Quebec. Meetings in January and June.

LA SOCIÉTÉ CANADIENNE-FRANÇAISE D'ELECTROLOGIE ET DE RADIOLOGIE MÉDICALES. *General Secretary*, Origéne Dufresne, M.D., Institut du Radium, Montreal. Meets third Saturday each month.

CUBA

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPIA DE CUBA. Offices in Hospital Mercedes, Havana. Meets monthly.

MEXICO

SOCIEDAD MEXICANA DE RADIOLOGÍA Y FISIOTERAPIA. *General Secretary*, Dr. Dionisio Pérez Couto, Marsella 11, México, D. F. Meetings first Monday of each month.

ABSTRACTS OF CURRENT LITERATURE

ROENTGEN DIAGNOSIS

The Head and Neck

The Chest

The Digestive System

The Musculoskeletal System

The Genito-Urinary System

RADIOTHERAPY

RADIATION EFFECTS

ROENTGEN DIAGNOSIS

THE HEAD AND NECK

Ectopic Pinealomas in the Chiasmal Region. Report of Three Cases. Gilbert Horrax and J. P. Wyatt. J. Neurosurg. **4:** 309–326, July 1947.

Three cases of so-called ectopic pinealoma in the chiasmal region are reported, all in Jewish boys between twelve and nineteen years of age. In 2 of the patients a primary pinealoma in the pineal region was present and verified microscopically. In one of these the chiasmal growth was shown to have come by direct extension from the pineal tumor through the wall of the third ventricle; in the other, such an extension was presumed but could not be verified. In the third patient there had never been any clinical evidence of a primary tumor in the pineal region. In 2 of the cases diabetes insipidus was the outstanding clinical complaint.

The chiasmal tumor was radically removed at operation in 2 instances. One patient is alive and well after four and one-half years. Postoperatively this patient was given 4,000 r through each of 3 portals directed at the suprasellar region for a total of 12,000 r over a three-month period. His physical, visual, and neurological status greatly improved and at the time of the report there was no evidence of recurrence of the tumor. The authors believe that radical surgery followed by roentgen irradiation would seem warranted in every such case.

Following Dorothy Russell's thesis that ectopic pinealomas are in reality teratomas (J. Path. & Bact. **56:** 145, 1944), serial studies on the material available were carried out in these 3 cases. In only one was there any suggestion of a teratomatous origin and here the visual proof was not conclusive. The other 2 cases represented classical pinealomas from the histopathologic aspect, with regional spread to the pituitary and hypothalamic regions in one.

Roentgenograms and photomicrographs are reproduced.

Movable Foreign Body within the Cerebral Ventricle. A Case Report. Leonard T. Furlow, Morris B. Bender, and H. Lukas Teuber. J. Neurosurg. **4:** 380–386, July 1947.

This case illustrates the rather free migration of a metallic foreign body within a lateral ventricle and also demonstrates the severe symptoms which may be associated with the presence of such a foreign body. A 22-year-old marine in June 1944 sustained several fragment wounds from the explosion of a Japanese shell, the major wound being situated in the right parietal region about 2 cm. above the ear. Amnesia followed the initial period of unconsciousness. A roentgenogram revealed a large piece of shrapnel in the superior portion of the right occipital lobe. Severe headaches, homonymous hemianopsia, convulsions, a progressive weight increase associated with an endocrine disturbance, and emotional instability developed over the next nine months. Roentgenograms taken during this time showed wandering of the shell fragment from its orginal position to just above the sella turcica. In May 1945, ventriculography showed definite dilatation of both lateral ventricles and indicated that the fragment was located in a dilated third ventricle. Removal of the foreign body was followed by an improvement in the patient's condition. Detailed studies of neurologic, psychiatric, and metabolic changes will form the basis for further reports. Roentgenograms are reproduced.

Congenital Arteriovenous Fistula Between the Internal Maxillary Artery and Pterygoid Plexus. Frank Gerbode and Emile Holman. Surgery **22:** 209–221, August 1947.

Congenital arteriovenous fistulas are attributed to a persistence of embryologic vascular channels. The effects of these abnormal communications upon the involved veins, arteries, and heart are the same as those associated with traumatic fistulas. Increased bone growth and other local effects are noted.

Details of the previously reported cases of congenital arteriovenous fistula of the face and neck are presented in table form and a further case is recorded. The patient was a six-year-old girl; the fistula was on the left, between the internal maxillary artery and the pterygoid plexus. There was a pulsating swelling below the left ear, the left mandible was enlarged, and the transverse diameter of the heart measured 9.5 cm., diminishing to 8.7 cm. following operation. The lesion was demonstrated by thorotrast carotid angiography. The surgical procedure, in which use was made of a muscle strip as an insert into the external carotid near the fistula, is described and illustrated. The immediate result was good. ALTON S. HANSEN, M.D.

The Vallecular Sign. Its Diagnosis and Clinical Significance. Julian Arendt and Arthur Wolf. Am. J. Roentgenol. **57:** 435–445, April 1947.

The dysphagia which accompanies many malignant growths of the hypopharynx and the upper stomach region is not, as commonly assumed, due to stenosis and prestenotic regurgitation, but is primarily a disturbance of deglutition. In these cases the "vallecular sign," consisting in the retention of barium in the pockets of the valleculae and in the pyriform sinuses, during swallowing, is of considerable importance. All patients with dysphagia should receive a barium meal and be examined with this sign in mind. Its presence is in favor of an organic lesion and is against a functional type of dysphagia.

A positive vallecular sign is demonstrated in carcinoma of the cardia, the hypopharynx, and the esophagus; also in bulbar paralysis and in myasthenia gravis. In one case of dysphagia lusoria due to abnormal origin of the right subclavian artery, the vallecular sign was the only positive roentgen finding.

The occurrence of the vallecular sign in myasthenia gravis and bulbar paralysis is not only helpful in their diagnosis but also in evaluating the therapeutic effect of thymus irradiation.

THE CHEST

War Wounds of the Chest. Roentgenological and Surgical Considerations. Henry L. Jaffe and Joseph P. O'Connor. Am. J. Roentgenol. **58:** 183–193, August 1947.

One hundred and sixty-five cases of chest wounds seen in a naval hospital are reported. All cases had had

previous treatment in the combat area. The roentgen findings are discussed under seven headings, as follows:

(*a*) *Normal Appearing Chest.* These cases showed clearing of previous hemothorax, re-expansion of wounded lungs, very little or no fibrosis from the tract of the missile, clearing of blast injury, and absorption of parenchymal hemorrhages.

(*b*) *Thoracic Cage Injury.*

(*c*) *Traumatic Hemothorax.* This was the commonest finding. Even with a large amount of lung compression only a slight mediastinal shift was noted. Most cases had had repeated aspirations without injection of air. No record of secondary hemorrhage following aspiration was found.

(*d*) *Pleural Thickening.* This may vary considerably in degree.

(*e*) *Lung Parenchyma.* Multiple areas of density due to hemorrhage following blast injury were noted. Massive pulmonary hemorrhage following penetrating wounds was seen. This is characterized by a generalized ground-glass appearance.

(*f*) *Bullet and Shrapnel Fragments.*

(*g*) *Injury to the Diaphragm.* Diaphragm injuries resulted in hernias of varying degree. In 2 cases there was complete retraction of the fragments of the diaphragm.

For purposes of definitive surgical care, the cases were divided into three groups: Class I, no further care; Class II, requiring treatment of necessity on admission; Class III, elective surgery.

The surgical procedures are discussed fully. In regard to hemothorax, the authors conclude that repeated aspirations are advisable and replacement with air is inadvisable. Aspiration should be started early.

Large foreign bodies were removed. Small fragments were left alone. It was found that small fragments do not result in abscess or excessive local reaction.

G. K. VOLLMAR, M.D.

Roentgenologic Diagnosis of Bronchiectasis Before Bronchography. C. Allen Good. M. Clin. North America **31:** 850–859, July 1947.

To determine how often a diagnosis of bronchiectasis could be made or suspected roentgenologically before bronchography was done, 123 cases of bronchiectasis were reviewed. Only those cases were included in the series in which the diagnosis was proved after the instillation of opaque oil into the bronchial tree or in which the lung was subjected to gross and microscopic examination after surgical removal or at necropsy.

The most common roentgen finding, an increase in the prominence of the pulmonary markings, was observed in 94 of the 123 cases. It was present alone in 39 cases, and in combination with one or more of the other roentgenologic signs of bronchiectasis in 55. Since bronchiectasis is commonly a disease of the lower lobes, these are the regions in which the increased markings are commonly present. When increase in pulmonary markings is present only in an upper lobe, the roentgen diagnosis is likely to be erroneous. Since tuberculosis most commonly involves the upper lobes and since the roentgen manifestations may resemble those seen in bronchiectasis, such a diagnosis is sometimes mistakenly made. Although an increase in pulmonary markings is the most common roentgen finding, it is the least dependable. Because a distinction between the normal and the abnormal is difficult in borderline cases, and because increased markings may be present in other conditions, a diagnosis of bronchiectasis will be made from the prebronchographic roentgenogram more often than can be justified by the frequency of occurrence of the disease.

Pneumonitis is seen roentgenologically in far fewer instances than on microscopic examination of tissue. In this series of 123 cases, 28 per cent showed roentgen evidence of frank pneumonitis. Its appearance was that of poorly circumscribed shadows or collections of shadows, frequently irregular, often dense but sometimes translucent.

Some degree of "honeycombing" was found in 26 per cent of the cases in the series. A significant decrease in volume of the affected lobe or portion of the lung was found in 15 per cent.

In 11 cases the roentgenograms of the thorax were considered normal. In 5 other cases nothing abnormal was recognized at the time the film was first seen, but a review disclosed one of the four signs mentioned above, usually obscured by the overlying shadow of the heart.

Although signs indicative of bronchiectasis were present in about 90 per cent of the 123 cases, actually the diagnosis was made 56 times and suggested 25 times. In the other 42 cases, a descriptive or erroneous report was given 26 times and a negative report 16 times.

Bronchography is necessary for a final unequivocal diagnosis of bronchiectasis and also to define the limits of involvement, particularly in those cases in which surgery is contemplated.

Routine Photofluorographic Examinations of Naval and Marine Corps Personnel: End Results. Sidney A. Britten and Wilbur V. Charter. U. S. Nav. M. Bull. **47:** 733–738, July–August 1947.

A Critique of Tuberculosis Control. Harold A. Lyons. Ibid, pp. 739–749.

A Review of 283,225 Chest Photofluorograms at the United States Naval Personne[1] Separation Center, Lido Beach, Long Island, N. Y. David F. Bew, Robert W. Tilney, Jr., and Walter E. J. Maher. Ibid, pp. 749–753.

Britten and Charter, in a review of the records of the U. S. Marine Corps and Navy personnel from April 1944 to March 1946, which includes the late war and early post-war period, found accumulated 1,843 cases of pulmonary tuberculosis in which the diagnosis was established during the study of those hospitalized because of suspicious findings in photofluorographic films confirmed in 14 × 17-inch films. A most interesting observation was that pulmonary tuberculosis was discovered somewhat earlier among enlisted men than among officers, due perhaps in part to a more uniform x-ray screening of the former at the beginning of their service and possibly to more frequent re-examinations. Another factor would seem to be the longer duration of service among officers. Approximately 35 per cent had service records of four years or longer as compared to 12.6 of enlisted personnel, a highly significant difference. This indicates that periodic chest examinations are more valuable the longer the period of service and supports the proposal for annual photoroentgen examination of all naval personnel regardless of rank or age. It is also pointed out that, while the immediate clinical significance of observed lesions may not appear to be great, these may subsequently become active, and that men showing such lesions should therefore be re-examined at shorter intervals.

Lyons points out that tuberculosis is still an important cause of death, especially in the early age groups. It ranks first for persons between the ages of twenty and forty. For this reason and because of the close living quarters, the disease is of special significance to the Navy. It is brought out that the diagnosis of tuberculosis, active or inactive, cannot be made from chest films alone, and that careless or hurried reading of photoroentgen or even 14 × 17-inch films increases the percentage of errors. Several cases illustrating the improper evaluation of roentgen evidence are presented. It is not the function of the radiologist to recommend re-examination, but to make known the presence of disease, leaving it to the clinician to discover its activity or to prove its inactivity. The methods for accomplishing this are briefly outlined.

In a series of 283,225 photofluorographic studies taken at a Separation Center as a regular part of the physical examination prior to discharge from the Navy, Bew and his associates found only 179 cases of confirmed tuberculosis, an incidence of 0.063 per cent. Details as to the disposition of the positive cases are included. SYDNEY F. THOMAS, M.D.

Routine Chest Roentgenograms of Hospital Admissions. G. Newton Scatchard and Diana Olga Duszynski. Dis. of Chest **13:** 312–318, July–August 1947.

A large number of unsuspected cases of tuberculosis will be found if a roentgenographic examination of the chest is made of all hospital admissions. In a fairly large number of admissions to the Edward J. Meyer Memorial Hospital in Buffalo from July 8, 1944, to March 12, 1945, evidence of pulmonary disease was found in 3.7 per cent of patients in whom there had been no suspicion of tuberculosis. The percentage of cases subsequently proved by sputum tests or at autopsy was 1.8.

The investigation was precipitated by the finding of an unduly high incidence of early tuberculous infiltration in student nurses. This was attributed to contact with unsuspected cases of the disease in noncontagious wards, and the observations here reported bear this out.

The authors regard miniature films highly. They believe that they are sufficiently good that they can be used for a large percentage of the usual original chest x-ray studies as well as follow-up examinations.

HENRY K. TAYLOR, M.D.

Unresolved Pneumonia. Ian Collins. M. J. Australia **2:** 68–69, July 19, 1947.

The author presents 2 case studies of unresolved pneumonia, a condition resulting from delayed resolution of lobar pneumonia. The etiology is unknown. The initial pneumonic process, which normally resolves either by crisis or lysis, is retarded for some unknown reason in about 4 per cent of cases. This state of unresolved pneumonia lasts several weeks to several months, when resolution takes place. Occasionally organization of the exudate occurs, leading to a condition of pulmonary fibrosis resembling chronic fibroid tuberculosis.

Two types of unresolved pneumonia are mentioned: (1) that in which temperature falls by crisis or responds rapidly to chemotherapy with persistent signs in the chest and (2) chronic pneumonia, in which temperature falls by lysis and the local signs remain, with slight irregular fever, occasional sweats, and rapid pulse rate.

X-ray findings confirm the diagnosis and are useful in following the progress of the disease and revealing other complications. Frequently small empyemata or pulmonary abscesses are detected radiographically and found to resolve together with the consolidation. Occasionally the condition terminates in fibrosis frequently accompanied by permanent collapse of the affected area.

Differential diagnosis of this condition from empyema, pleurisy, tuberculous lobar pneumonia, and bronchogenic carcinoma is briefly but thoroughly discussed. Prognosis is considered fair. Treatment consists of chemotherapy, diathermy, and supportive measures. SAVA M. ROBERTS, M.D.

Disseminated Chickenpox (Pneumonia and Nephritis). Charles E. Grayson and Elizabeth J. Bradley. J. A. M. A. **134:** 1237–1239, Aug. 9, 1947.

A case of chickenpox associated with pneumonia and nephritis is presented without demonstrable pathogenic bacteria in the upper part of the respiratory tract or in the circulating blood. Proof that both the pneumonia and the nephritis were due to a virus infection (in this case, chickenpox) was obtained by various laboratory and clinical tests. The pneumonic densities seen on the roentgenograms coincided with the course of cutaneous manifestations. Furthermore, response to sulfadiazine or penicillin therapy by clinical improvement or lowering of temperature was lacking. No pathologic bacteria could be recovered from the blood or samples of the sputum. Reactions to agglutination tests helped to rule out at least one of the more frequent and one of the less frequent forms of virus pneumonia. Nephritis, which was not present before or shortly after sulfadiazine therapy, developed on the twenty-eighth hospital day, and this too was believed to be a manifestation of the chickenpox virus. It is felt that the addition of this case, and others with detailed clinical studies, might assist in the possibility of better differentiation of pathologic entities. ANDREW K. BUTLER, M.D.
(University of Michigan)

Primary Carcinoma of the Lungs, with Invasion of the Ribs. Pneumonectomy and Simultaneous Block Resection of the Chest Wall. Frank Philip Coleman. Ann. Surg. **126:** 156–168, August 1947.

The purpose of this paper is to question the relegation of cases of lung carcinoma invading the bony thorax to an incurable group.

The incidence of chest wall invasion is probably between 5 and 10 per cent of all cases of carcinoma of the lung. A review of the published cases of Pancoast tumors, which have as one clinical feature local and adjacent destruction of a rib, showed the majority to be squamous-cell carcinomas of peripheral bronchogenic origin. In the author's series of cases, invasion of ribs was limited to carcinomas of squamous-cell type.

The behavior of peripheral squamous-cell carcinomas is not unlike that of the more centrally placed tumors of this variety. They invade contiguous structures, infiltrate, grow slowly, and metastasize late in the course of the disease. This favorable pathological behavior renders such tumors amenable to radical cancer surgery. Treatment consists of block resection of the chest wall, total pneumonectomy, and removal of the regional

lymph nodes. Although such treatment will probably increase the mortality rate in general for cancer of the lung, that seems of little importance when the prognosis for this particular group is considered.

Seven cases are reported, in 5 of which block excision of the chest wall and pulmonary resection were done. A total pneumonectomy was carried out in 4, and a palliative lobectomy in 1. There was 1 operative death. The patient in whom a palliative lobectomy was done died eleven months postoperatively. The remaining 3 patients are alive and well, one for six years, one for two years, and one for five months.

M. WENDELL DIETZ, M.D.

Pulmonary Resection for Solitary Metastatic Sarcomas and Carcinomas. John Alexander and Cameron Haight. Surg., Gynec. & Obst. **85:** 129–146, August 1947.

The authors point out that the appearance of a presumed solitary metastatic lesion in a lung months or years after apparent complete removal of a primary extrapulmonary sarcoma or carcinoma is far from rare. If untreated surgically, these patients almost invariably die, usually from invasive, infectious, or pressure effects of enlargement of the original metastatic lesion and from other metastases.

A search of the literature revealed only 5 case histories in which both primary and metastatic lesions were removed. This paper includes 13 more case histories from various clinics and 6 from the authors' experience.

Of this collected series of 24 cases, 16 were carcinomas and 8 sarcomas. Of the 24 patients, 11 have had recurrences; 1 died as a direct result of the operation, and 12 are apparently free of recurrence. Among these last, however, are 4 in whom pulmonary resection was performed less than a year ago. The interval since operation in the remainder ranges from one to twelve years. Six of the patients now apparently well had carcinoma and 6 sarcoma.

It is made clear that surgical removal of a metastatic malignant neoplasm assumed to be solitary is a gamble, but with failure to remove the lesion death will inevitably ensue. It is also pointed out that not all tumor shadows in the lung at the time of, or following, removal of a primary lesion are metastatic, and in some of the cases reported the surgeons were unable to reach a decision on this point preoperatively.

Removal of a presumably solitary pulmonary metastasis should be attempted only if physical and roentgen examination have excluded other metastases, if there is reasonable assurance that the primary lesion was completely removed, and if the patient's physical condition is such as to warrant pulmonary surgery. In general, a late metastasis is believed to offer a better prognosis than one appearing early after removal of the primary tumor.

The twenty-four cases histories are included.

RICHARD C. RIPPLE, M.D.

Carcinoma of the Pancreas with Pulmonary Lymphatic Carcinomatosis Simulating Bronchial Asthma: Case Report. Charles F. Sweigert, Edward F. McLaughlin, and Erle M. Heath. Ann. Int. Med. **27:** 301–308, August 1947.

This case report illustrates the occurrence of bronchial asthma secondary to pulmonary lymphatic metastasis and the association of the latter with primary abdominal cancer. In addition, the age of the patient, 22 years, is unusual, and the duration of the entire illness (two months) was strikingly brief.

Increased serum amylase maintained over a period of several weeks, though not typical of an acute pancreatitis, suggested pancreatic involvement. The age of the patient, the dry cough, râles and wheezes, and the chest roentgenogram (dissemination in both lung fields of infiltrations of increased density) suggested the possibility of either tuberculosis, silicosis, sarcoid or Hodgkin's disease. The progressive development of jaundice focused attention on the biliary system. Weight loss (15–20 lb. within eight weeks), a firm palpable mass in the epigastrium, the jaundice, the wide duodenal loop demonstrated roentgenographically, and the pulmonary symptoms and signs, if assumed to be due to one disease process, could be explained only on the basis of a neoplastic mass in the region of the upper gastro-intestinal tract with metastasis to the lungs. The preoperative diagnosis was: intra-abdominal malignant growth, probably pancreatic, with lymphatic metastasis to the lungs.

An exploratory laparotomy was performed, and the pancreas was found to be replaced by a firm nodular mass. Due to the extensive involvement, definitive surgery was out of the question. The postoperative course was characterized by progressive failure, weakness, pain, increasing respiratory distress and emaciation. At this time constant diffuse sibilant râles and asthmatic wheezes were heard throughout both lung fields, presenting the clinical picture of severe, intractable bronchial asthma. The patient had frequent severe paroxysms of cough and marked dyspnea and wheezing, plainly audible at a distance. He failed rapidly and died two months after the first symptoms.

Necropsy showed diffuse metastatic involvement of the lungs, bronchial lymph nodes, liver, adrenals, and vertebrae. Microscopic sections of the pancreas consisted almost wholly of infiltrating adenocarcinoma.

STEPHEN N. TAGER, M.D.

Adenomas Arising from Small Bronchi Not Visible Bronchoscopically. Herbert C. Maier and Walter W. Fischer. J. Thoracic Surg. **16:** 392–398, August 1947.

Up to the present time all reports on bronchial adenoma have stated that they are located in the larger bronchi, and the diagnosis can be established by bronchoscopy and biopsy. The authors present 5 cases in which these tumors arose from secondary bronchi not visible by bronchoscopy. One of these patients had hemoptysis and one had chest pain. The others were asymptomatic. There were 3 females and 2 males. The ages ranged from sixteen to forty-two. The roentgenograms showed well circumscribed rounded nodules about 4 to 6 cm. in diameter, four of them being near the hilus and one at the base posteriorly. The tumor resembles a large solitary metastasis. All were removed surgically with good results.

HAROLD O. PETERSON, M.D.

Intralobar Sequestration of Lung Associated with an Abnormal Pulmonary Artery. D. M. Pryce, T. Holmes Sellors, and L. G. Blair. Brit. J. Surg. **35:** 18–29, July 1947.

Pryce in 1946 described a condition in which an abnormal artery was associated with an ectopic pulmo-

nary mass in the lower lobe (J. Path. & Bact. **58:** 457, 1946). The abnormality was twofold, consisting in: (1) a large artery to the lung from the aorta in the region of the diaphragm and (2) a congenital bronchopulmonary dislocation (sequestration or ectopia) in the part supplied by the abnormal artery. Previous reports of the dual abnormality are very scanty but the arterial abnormality alone has been more often recorded. It is possible that the bronchopulmonary abnormality was overlooked.

Three types of arterial abnormality may be recognized: (1) abnormal artery to normally connected lung; (2) abnormal artery to sequestrated mass and adjacent normal lung; (3) abnormal artery confined to the sequestrated mass. These abnormal arteries are large and have the elastic structure characteristic of pulmonary arteries. In all instances the vessel appears to arise from the lower part of the thoracic aorta or upper part of the abdominal aorta. Cases with sequestration have been more common on the left and those without sequestration have been more common on the right.

The intralobar sequestration varied in appearance in the cases reported. In several cases it took the form of a large cyst. In one case it was a mass of polycystic lung connected with a dislocated blind bronchus at the hilum. In one case the mass was disorganized by sepsis and consisted of irregular epithelized spaces communicating with similar spaces in the adjacent lung. Although incorporated within the lower lobe, the sequestration was dissociated from the normally connected lung. In some cases the dissociation was complete but in others the bronchial tree communicated with the sequestration. In all cases the sequestration was located in the posteromedial part of the lower lobe and by its own size reduced that of the posterior or even all three basal sectors. This reduction in the space available for growth of adjacent lung was sometimes shown in bronchograms.

Inflammatory changes varied greatly. In 3 cases inflammation was slight and in 3 cases there was dense fibrosis. Infection probably occurs by direct spread from a pneumonic process in the adjacent lung.

The clinical symptoms were all referable to infection, which tended to begin in early life. In the 8 reported cases the age at onset varied from twelve to twenty and age at operation from thirty-three to forty. The initial symptoms were those of pneumonia, which usually subsided. In some cases there was a repetition of the pneumonic process, even progressing to suppuration. Emphysema and bronchiectasis were diagnosed in two cases. Drainage in these cases was not followed by obliteration of the cavity as this was epithelized.

Preoperative diagnosis of this condition is difficult, though radiological examination and bronchography may suggest the possibility of its presence. A dense shadow at the base of the lung is suggestive but not pathognomonic. In one case with a drainage tube the instillation of opaque oil filled the sequestrated bronchial tree. The most suggestive feature is the incomplete filling of the adjacent bronchial tree, which may be apparent in the absence of crowding.

The treatment of the condition is operative excision and, since preoperative diagnosis is rare, the presence of the condition should be borne in mind in any surgical procedure in this part of the thorax. The ultimate result of excision in all cases was satisfactory.

The authors add a lengthy description of the development of this abnormality which is obviously related to lower accessory lung. The related abnormalities associated with an abnormal blood supply from the dorsal aorta to the lung at different stages of its development are well illustrated by diagrams. For those interested, the discussion of the embryology is well worth reading.

Eight illustrative case reports are included.

MAX CLIMAN, M.D.

Clinical Syndrome Associated with Pulmonary Arteriovenous Fistulas, Including a Case Report of a Surgical Cure. Howard B. Burchell and O. Theron Clagett. Am. Heart J. **34:** 151–162, August 1947.

The fact that the clinical syndrome of cyanosis, clubbing of the fingers and toes, and polycythemia may be associated with an arteriovenous shunt in the lesser circulation is very important, since recent advances in thoracic surgery have made possible complete cure of this condition with a minimal operative risk. The roentgen examination discloses a nodular appearing pulsating lesion and increased hilar pulsation on the same side. It also discloses the size and location of the fistula and indicates whether more than one is present.

The authors report a case with the unusual complication of collateral circulation to the thoracic wall. The patient was a 20-year-old student who was referred for surgical treatment for a cyanotic disorder of the circulation. He had been a normal appearing baby and not until the age of eight was it observed that his lips were darker than those of other children. While he was still in the grades he complained of aching pains in his legs, and clubbing of the fingers was observed. Shortness of breath was denied except in recent years. The knee, wrist, and ankle joints were enlarged, and superficial ulcerations were present on the medial aspects of the ankles. The spleen was enlarged. The roentgenographic examination revealed an irregular, nodular, pulsating lesion adjacent to the inferior portion of the right hilum, thought to be a vascular abnormality within the right lobe. Laboratory findings supported a diagnosis of pulmonary arteriovenous fistula.

Lobectomy was performed. Examination of the excised lobe showed it to consist of two parts, a medial portion, which was normal and could be inflated, and a lateral portion consisting of a mass of twisted varicose vessels, which could not be inflated. The patient was discharged on the seventeenth postoperative day, feeling well and with a normal color. Ten weeks after operation he had no complaints. His fingers and toes showed little change. The dermatitis of the ankles had healed, leaving a normal appearing skin with slight pigmentation. A roentgenogram showed some decrease in the heart shadow, though this had been well within normal limits prior to operation. The patient had not indulged in any strenuous activity and had not noticed any change in exercise tolerance.

HENRY K. TAYLOR, M.D.

Anomaly of Aorta Simulating Mediastinal Tumor. David B. Corcoran and Frank Philip Coleman. J. Thoracic Surg. **16:** 427–431, August 1947.

A 58-year-old man complained of weakness, "colds," pains in the chest, and slight weight loss. He had a blood pressure of 172 mm. Hg systolic and 110 mm. diastolic. A chest film showed a "mass" along the left of the spine from the 7th rib to the 10th with a convex border bulging into the left chest. The lower end of the

esophagus was displaced anteriorly and to the left. Pulsation could not be accurately determined fluoroscopically. The mediastinum was explored and a tortuous aorta was found accounting for the mass. Recovery was uneventful. The films appear quite typical of the so-called "low right-sided aorta" due to tortuosity. The authors feel that a congenital anomaly is a better explanation for this aorta than the usual explanation of the tortuosity and elongation so frequently encountered in older people. They present two possible embryological origins for this condition.

HAROLD O. PETERSON, M.D.

Mediastinal Tumor. Jacob K. Berman, J. Paxton Powell, and Philip C. Hennessee. Am. J. Surg. **74:** 205–210, August 1947.

The authors discuss very briefly the theories as to the pathogenesis of mediastinal tumors, with emphasis on teratomas. A simple classification of the types of tumor is given. Included are various types of cystic, vascular, and pericardial tumors, hyperplasia and neoplasm of the thyroid, parathyroid, thymus, connective and nervous tissue, of lymph nodes and of the trachea and esophagus. It is conceded that teratomas behave erratically, growing or remaining quiescent for years. Usually they grow as the child grows and become stationary after maturity, barring such complications as trauma, infection, or rarely malignant change. One of the two tumors reported by the authors appeared to keep pace in growth with the child. The other was discovered in early life and was, therefore, small.

The signs and symptoms are mainly due to increase in mediastinal pressure, to displacement of organs, and to the site of the tumor. There may be interference with blood flow return through the superior vena cava resulting in cyanosis, orthopnea, dilatation of superficial veins, pulmonary edema, pleural and pericardial effusions. Posterior tumors, such as ganglioneuroma, are apt to affect the cervical sympathetic, causing a Horner's syndrome. Persistent cough, with or without hemoptysis and dyspnea, are the most common symptoms of dermoids and teratomas. Dysphagia, hematemesis, asthma, or pneumonia may also occur. Occasionally there are no symptoms and the growth may be an incidental finding.

Among the aids in diagnosis, roentgenology is stressed. It is of value in localizing the tumor, in revealing the presence within it of unusual shadows, and in determining whether or not there is pulsation and whether the spine or ribs are involved. Roentgen therapy is employed in some cases as a therapeutic test. Tumors in the anterior mediastinum are usually dermoids and teratomas; mid-mediastinal tumors are usually lymphoblastomas; those in the posterior mediastinum, neurofibromas or other nerve tissue growths.

One of the authors' patients was a fifteen-year-old boy with a huge mass in the anterior mediastinum. The symptoms were severe pain in the chest, cough, and dyspnea. Failure of response to irradiation ruled out the probability of lymphoblastoma and at operation, a teratoma was removed. The other patient was a four-year-old girl, in whom a tumor in the left anterior mediastinum was incidentally discovered by x-ray. The child was free of symptoms. At operation a cystic tumor with a very vascular attachment to the hilum of the left lung was removed. This also proved to be a teratoma.

DAVID S. MALEN, M.D.

Intrusion of Aortic Root into Mitral Orifice in Hypertensive Disease: Radiologic Observations on Living Persons. Frank Windholz and Charles E. Grayson. Am. Heart J. **34:** 180–187, August 1947.

The annulus fibrosus does not completely encircle the mitral ostium, but is located only on the anterior, lateral, and posterior aspects. The mitral ring is completed by the posterolateral portion of the aortic ring and contiguous structures. Roentgenologically the calcified mitral annulus fibrosus appears as a horseshoe-shaped structure. Only when the adjacent aortic ring is also calcified is the mitral orifice completely surrounded by a continuous circular or ellipsoid calcific deposit.

Variations in the size and shape of the aortic root may influence the shape of the mitral orifice. In three cases of hypertensive disease seen by the authors, the root of the aorta intruded into the mitral ostium and produced a loss of the cross-section area of the latter. In these cases the ring surrounding the mitral orifice was not circular or ellipsoid but crescent-shaped, the greater or posterolateral segment of the crescent representing the calcified annulus and the smaller or anteromedial segment the posterolateral portion of the aortic ring. Radiologic demonstration in these cases was possible only because there were extensive calcifications of both the mitral annulus fibrosus and of the aortic ring. It is believed that similar protrusion of the aortic root into the mitral ostium may often occur in hypertensive disease though in the absence of calcification it may not be demonstrable radiologically.

The possibility of functional changes as a result of encroachment of the aorta upon the mitral orifice must be considered, though the narrowing of the orifice must be very considerable before it produces a significant mechanical obstacle to the circulation. The authors quote Allan (Heart **12:** 181, 1925) as finding that "a loss of 75 per cent of the cross section of the mitral ostium reduces the inflow to the ventricle a little, and that this reduction is easily overcome by a rise of the blood pressure." The estimated loss of the cross-sectional areas of the mitral orifices in the authors' three cases were 35–40, 50–55, and 60–65 per cent.

HENRY K. TAYLOR, M.D.

Electrokymograph for Recording Heart Motion, Improved Type. George C. Henny, Bert R. Boone, and W. Edward Chamberlain. Am. J. Roentgenol. **57:** 409–416, April 1947.

Roentgen Elektrokymography. W. Edward Chamberlain. Acta radiol. **28:** 847–858, Nov. 13, 1947.

An electrokymograph, which has been considerably improved and simplified over the first apparatus devised by Henny and Boone (Am. J. Roentgenol. **54:** 217, 1945. Abst. in Radiology **47:** 88, 1946), is described. This device consists of a clinical fluoroscope, a 931-A (or equivalent) multiplier phototube with its necessary power supply, a selective filter to absorb the alternating current ripple in the roentgen beam while passing the significant current fluctuations that are to be recorded, some form of recording galvanometer, and a means for the simultaneous registration of some such time-reference curve as the carotid sphygmogram, an oscillogram of the heart sounds, or an electrocardiogram.

Sample electrokymographs are reproduced in both papers.

Right-Sided Thoracic Stomach. J. George Teplick and Stanley H. Macht. Am. J. Roentgenol **58:** 196–202, August 1947.

Six cases of right-sided thoracic stomach in adults are reported. All were of the non-traumatic type, and all were probably of congenital origin. In four cases the stomach passed through the esophageal hiatus; in one no right diaphragm could be recognized on the films or fluoroscopically. In the sixth case no lateral views were available to indicate through what portion of the diaphragm the stomach passed.

None of the patients had severe or progressive gastrointestinal symptoms. Three had had mild symptoms since childhood, while three were asymptomatic.

In all cases the diagnosis was suspected from routine roentgenograms of the chest five of these were miniature chest films taken in surveys.

A rounded density in the right lower chest, with or without gas-bubbles, and absence of the gastric gas-bubble under the left diaphragm were the characteristic findings.

G. K. VOLLMAR, M.D.

THE DIGESTIVE SYSTEM

Roentgenograms of Thorax That Suggest Carcinoma of Stomach. B. R. Kirklin and Eva L. Gilbertson. J. A. M. A. **134:** 1228–1230, Aug. 9, 1947.

Malignant lesions at the cardia of the stomach are discussed, and the criteria for fluoroscopic evidence of such a lesion are outlined. Among others is included the presence of polypoid growths which project as rounded prominences and cause deviation of the path of the barium. In many instances the lesion can be recognized, or at least strongly suspected, as the patient stands behind the screen, before the opaque meal is given. A tumefactive mass projecting from the medial wall into a stomach gas bubble is sometimes encountered.

Furthermore this gas bubble, visible in the majority of cases in an ordinary roentgenogram of the thorax, will often demonstrate the presence of a mass projecting into it. An analysis of 68 cases of tumor of the cardiac portion of the stomach seen on roentgenoscopic examination showed that at least half of these could be suspected from roentgenograms of the thorax.

ANDREW K. BUTLER, M.D.
(University of Michigan)

Gastric Carcinoma; Can an Increased Diagnostic Accuracy Greatly Improve Survival Rates? Frederic E. Templeton. J. Nat. Cancer Inst. **7:** 385–386, April 1947.

Patients with gastric carcinoma stand a 1 to 5 per cent chance of a five-year survival. If, however, the primary lesion is resectable, the figure rises to 15 to 32 per cent. It is said that four-fifths of all patients dying from cancer of the stomach have distant metastases at autopsy and that only 10 per cent of patients seen on the operating table are free from metastases. These figures indicate that any hope of spectacular improvement in survival rates lies in discovery of the lesion before it is beyond resectability and before metastasis to distant sites has occurred. We do not know, however, how the majority of carcinomas grow, or whether detection is possible before metastases have occurred. Until these phases of the problem are solved, mass surveys and increased diagnostic accuracy with present-day methods will not increase greatly the percentage of five-year survivals.

LOUIS BERNSTEIN, M.D.

Pernicious Anemia and Tumors of the Stomach. Leo G. Rigler and Henry S. Kaplan. J. Nat. Cancer Inst. **7:** 327–332, April 1947.

An Attempt to Identify Likely Precursors of Gastric Cancer. David State, Richard L. Varco, and Owen H. Wangensteen. J. Nat. Cancer Inst. **7:** 379–384, April 1947.

Rigler and Kaplan review at length the literature indicating the frequent association of gastric carcinoma and pernicious anemia and suggesting that these two diseases may be linked indirectly through the medium of some common factor. Mass gastro-intestinal surveys of healthy persons have yielded a minimum of tumors and have indicated the necessity of some criterion for selecting patients for routine periodic examination of the stomach. Pernicious anemia is believed to meet this requirement.

In 1945 the authors presented the results of serial roentgenologic and gastroscopic examination of 211 patients with pernicious anemia, of whom 8 per cent were found to have gastric carcinoma and 7 per cent benign polyps (J. A. M. A. **128:** 426, 1945. Abst. in Radiology **46:** 427, 1946). Since then, 48 new cases of pernicious anemia have been examined at the University of Minnesota, yielding 1 additional gastric cancer and 2 cases of benign polyps. Comparison of these results with the morbidity of gastric cancer in unselected cases of comparable age reveals clearly the striking concentration of carcinomas of the stomach in patients with pernicious anemia.

Unfortunately, pernicious-anemia patients represent a very small fraction of those susceptible to gastric cancer. Other indicators must be determined by careful clinical studies on large groups of variously categorized patients. Preliminary results of such a study by State, Varco, and Wangensteen suggest achlorhydria as another probable precursor of gastric cancer. These authors are continuing their study on patients with gastric polyps and pernicious anemia, on relatives of patients known to have gastric cancer, and other groups.

Duodenal Obstruction in the Newborn, with a Description of Four Cases. Isabella Forshall. Brit. J. Surg. **35:** 58–69, July 1947.

Following a complete historical description of duodenal obstruction in the newborn, beginning with a report of a case by Calder in 1752 and a brief outline of case reports up to 1939, the author presents an excellent anatomical and embryological discussion. Duodenal obstruction may be intrinsic or extrinsic. Intrinsic obstruction may be caused by: (*a*) complete discontinuity of the duodenum; (*b*) a condition in which the dilated proximal duodenum is joined to the collapsed distal duodenum by a fibrous cord; (*c*) narrowing of the duodenal lumen for a variable length; (*d*) presence of a diaphragm, either complete or incomplete, in the duodenal lumen.

Extrinsic obstruction is more common than the intrinsic variety and in the majority of cases the site of the obstruction is in the distal duodenum at or near the duodenojejunal junction. This type of obstruction can be caused by a variety of conditions, but the majority of cases are due to some abnormality of intestinal rota-

tion. The duodenum is compressed or dragged upon by abnormal peritoneal bands or there is a volvulus of part or the whole of the midgut loop.

The dominant symptom is vomiting which begins within thirty-six hours of birth and soon becomes projectile in type. Bile is present in the vomitus when the obstruction is distal to the biliary papilla. In untreated cases the child becomes increasingly apathetic and life is seldom prolonged beyond the twelfth day. Occasionally children may survive a long time in cases of intermittent volvulus or where the lumen is narrowed.

Radiological examination will confirm the diagnosis and give information as to the site of the obstruction. The scout film of the abdomen will reveal air-filled stomach and duodenum above the obstruction. The collapsed bowel below the obstruction contains no gas and is not outlined. A roentgenogram which shows the colon in an abnormal position and the small bowel bunched in the right side of the abdomen suggests an extrinsic obstruction due to faulty rotation. An oblique view often will reveal the distended duodenum.

The various operative procedures for intrinsic obstruction are described in detail. Anastomosing operations, short-circuiting the obstruction, have been used in the majority of successful cases. The possibilities are a gastrojejunostomy, a duodenojejunostomy, or a duodenoduodenostomy. A gastrojejunostomy is the easiest to perform. In extrinsic obstruction the volvulus is untwisted, or, if this cannot be done, a short-circuiting anastomosis is performed.

Four complete case reports are added with reproductions of roentgenograms in 2 cases and of a specimen of 1 case. Three cases were of intrinsic type and one was extrinsic. In the intrinsic cases the obstruction was above the ampulla of Vater in 2 cases, below in 1 case. In the extrinsic case obstruction was complete. There was a volvulus of the whole of the small intestine and non-rotation. Two patients died and two are alive and well.

MAX CLIMAN, M.D.

Congenital Absence of Gallbladder. Report of Three Cases. Earl O. Latimer, F. L. Mendez, Jr., and W. J. Hage. Ann. Surg. **126:** 229–242, August 1947.

Three additional case reports of congenital absence of the gallbladder are presented by the authors. Seventy cases from the literature, verified either at operation or autopsy, are also reviewed.

A preoperative diagnosis is extremely difficult, if not impossible. There is no group of symptoms or signs which are of value in recognizing the anomaly, and it is so rare that it is not usually suspected when cholecystographic tests reveal total non-filling. An intrahepatic gallbladder may be ruled out by retrograde cholangiography if the viscus cannot be found at operation. This was done in one of the authors' cases.

An attractive theory accounting for absence of the gallbladder involves the embryology of the biliary tree. From the floor of the future duodenum arises the hepatic diverticulum. A cranial portion is the anlage of the bile ducts, a caudal portion is to become the gallbladder and the cystic duct. Though the hepatic diverticulum is originally tubular, the biliary passage tends to become solid, and a lumen is not re-established until the seventh week. Thus, failure of the gallbladder anlage to form or failure of the solid anlage to become tubular would result in absence of the gallbladder.

M. WENDELL DIETZ, M.D.

THE MUSCULOSKELETAL SYSTEM

Appearance and Growth of Ossification Centers and Increases in the Body Dimensions of White and Negro Infants. Harriet J. Kelly and Lawrence Reynolds. Am. J. Roentgenol. **57:** 477–516, April 1947.

Four hundred and twenty-five infants (174 white males, 131 white females, 55 negro males, 65 negro females) were observed at approximately twenty-eight day intervals during their first year of life. Some were followed through their second and third years. Data for those years are included in the present paper but no conclusions are drawn from them. At each examination, in addition to other studies, roentgenograms were obtained for measuring areas and dimensions of bone structures and various external measurements were made. The norms for the entire group of infants were established, and the data were separated as to race and sex to determine whether there were significant differences between infants of the negro and white races.

The white male babies were on the average longest as indicated by the recumbent length values (total, stem, head, and trunk), widest in the head, chest, and hips, and had the greatest expanse and density as measured by circumference of head and chest and by weight. The negro male babies were observed to be the largest according to depth of chest, length of tibia, and girth of upper arm. The negro females were the shortest group according to the recumbent length and narrowest according to width of chest and hips. The white females were shortest in head length and tibial length, narrowest in chest depth, smallest in circumference of abdomen, head, chest, and upper arm, and weighed the least of the four groups.

The per cent of wrist size ossified, as measured by the total carpal area per unit of wrist area, was greatest for the negro females, least for the white males. The negro males and white females were not consistent in relative standing for the various age levels.

The widths of the radius and tibia at their metaphyses, and of the diaphysis of the tibia one-third of its length above the distal end, were smallest for the white female infants, followed by the negro females and white males; the negro males had the greatest dimensions at most age levels. The lengths of the radius and the tibia were smallest for the white female group, next for either the white males or negro females, and largest for the negro male infants. The white males had the smallest average width of epiphyses of the radius; the negro males came next, then the white females, and finally the negro females, with epiphyses of the greatest average width.

Of the four carpal bones present during the first year, the capitate appeared first, the hamate second, the triangular third, and the lunate fourth.

The calcaneum and astragalus were present in every case, but of the remaining tarsal bones, the cuboid appeared first, the external cuneiform second, the internal cuneiform third, the middle cuneiform and scaphoid fourth and fifth, respectively.

Of the nineteen bones of the hand, the epiphyses of the second and third metacarpal, of the second, third, and fourth proximal phalanges, and of the first distal phalanx were among the first to appear. The average ranking of each of the epiphyses of the hand varied only slightly from one race or sex group to another.

The ten epiphyses of the five metatarsals and proximal phalanges varied in order from one group to an-

other, though the epiphyses of the first metatarsal and of the second, third, and fourth proximal phalanges were always among the first to appear.

The distal epiphyses of the femur, tibia, fibula, radius, and ulna, the proximal epiphyses of the tibia, fibula, and radius, and the capitellum were ranked in order of appearance. Of these the distal epiphysis of the femur appeared first and the proxmal epiphysis of the tibia appeared second in all cases. The distal epiphyses of the tibia and capitellum shared honors for third and fourth places.

An Epidemic of Inhalation Lead Poisoning with Characteristic Skeletal Changes in the Children Involved. George Cooper, Jr. Am. J. Roentgenol. **58:** 129–141, August 1947.

An outbreak of lead poisoning occurring in a group of children all living in one neighborhood is discussed. Discarded storage battery cases had been used for fuel in almost all of the homes in this area and inhalation of the fumes was considered as the cause.

Nineteen persons were examined, ranging from 3 months to 21 years of age. All but 4 of these showed abnormal metaphyseal densities and 2 of these 4 showed other evidences of lead poisoning. The skeletal changes were more prominent in the younger children. There was absence of gastro-intestinal symptoms in most cases. There was little correlation between the skeletal deposits and toxic symptoms. The staining of the necks of the teeth with lead sulfide showed the closest correlation with the skeletal findings. Red blood cell stippling was present in only one-third of the cases. Roentgenographically the usual increased metaphyseal densities were found.

It is concluded that roentgen changes due to lead are identical, whether the absorption is by way of the respiratory tract or the gastro-intestinal tract. Roentgen evidence of skeletal deposits does not occur earlier than three months from inhalation and probably six months from ingestion. Teeth staining is an important sign in children; when it is associated with cerebral signs, gastro-intestinal symptoms, or muscular pain and weakness, the skeleton should be examined by x-ray.

G. K. VOLLMAR, M.D.

Soft Tissue Changes in Early Acute Osteomyelitis. George J. Baylin and John C. Glenn, Jr. Am. J. Roentgenol. **58:** 142–147, August 1947.

The authors believe that soft-tissue changes can be noted in acute osteomyelitis sometimes as early as twenty-four hours after onset of the disease. These changes consist of (1) roughening of the usually sharp line of demarcation between the subcutaneous shadow and the muscular bundles; (2) obliteration of the intermuscular cleavage planes. These changes extend along the entire extent of the involved bone even though the bone lesion may be in the extreme end of the bone. After evidence of bone changes develops, with periosteal reaction and a break in the cortex, the soft-part changes tend to regress.

Comparison is made with the soft-tissue changes noted in sprains, abscesses, tumors, and other lesions. All of these show localized soft-tissue changes only, without a tendency to involve the soft tissues overlying the entire extent of the bone, as in acute osteomyelitis.

The increased intra-osseous pressure existing in early osteomyelitis probably accounts for the changes, possibly secondary to extravasation of fluid through the haversian canals. This explains the regression of the soft-tissue changes following relief of the intra-osseous pressure by a break in the cortex of the bone.

The authors conclude that the findings described are characteristic and believe that soft-tissue roentgen studies should be done on every case of suspected osteomyelitis.

G. K. VOLLMAR, M.D.

Secondary Hypertrophic Osteoarthropathy in Congenital Heart Disease. Myron G. Means and N. Worth Brown. Am. Heart J. **34:** 262–271, August 1947.

The authors report a case of hypertrophic osteoarthropathy associated with uncomplicated congenital heart disease. The patient, 26 years of age, had been cyanotic during his entire life. Deformities of the wrists and ankles were noticed at the age of twelve, and periodic pain in these joints occurred during adolescence. Physical examination revealed moderate general cyanosis, most conspicuous in hands and feet. These showed marked clubbing, and there were irregular soft-tissue swellings about the wrists and ankles. The hands presented a claw-like appearance. The lower legs suggested the "elephant foot" described in the earliest accounts of secondary osteoarthropathy. They also showed patches of dark purple discoloration. There were no findings to indicate chronic pulmonary disease. The heart did not appear to be appreciably enlarged, but there was increased manubrial dullness. A double systolic impulse was felt over the precordium and was visible in the vessels of the neck. A loud systolic murmur was heard, transmitted to the right. A second systolic murmur was also heard, of higher pitch and different quality, not accompanied by a thrill.

Roentgenograms of the extremities disclosed symmetrical hypertrophy of the radii, ulnae, tibiae, and fibulae, slight roughening of the interosseous margins of the radii, ossifying periosteal new bone formation on the tibia; and osteophyte irregularities as well as hypertrophy of several points of tendon and ligament insertion, notably at the radial styloids, external tibial tuberosities, and the internal malleoli. The tufts of the terminal phalanges of the hands were smooth; those of the toes showed partial resorption. There was no evidence of disease of the pleura, lungs, mediastinum, or spine. The heart, according to measurements, showed a 14 per cent increase in size over that predicted. The right hilum was prominent and showed an increased amplitude of pulsation. The vascular markings were accentuated.

The history, physical findings, and electrocardiogram led to the diagnosis of congenital heart disease of the Fallot type. Following establishment of an anastomosis between the right common carotid and right pulmonary arteries, dyspnea was relieved and cyanosis diminished. Within six weeks the deformities about the hands and feet became less marked. This shows that some of the changes associated with secondary osteoarthropathy are reversible, and lends support to the view that the dynamics of the circulation have a part in their production.

HENRY K. TAYLOR, M.D.

Osteoporosis Associated with Low Serum Phosphorus and Renal Glycosuria. W. T. Cooke, J. A. Barclay, A. D. T. Govan, and L. Nagley. Arch. Int. Med. **80:** 147–164, August 1947.

In the case of a 39-year-old man with progressive osteoporosis, laboratory and necropsy findings sug-

gested that a functional defect of the renal tubules led to a persistently low serum phosphorus and that this was the cause of the osteoporosis. Six similar cases have been reported in the literature. These cases offer support for Hunter's hypothesis (Proc. Roy. Soc. Med. **28:** 1619, 1935) that osteoporosis may on occasion be due to a renal defect unassociated with signs of chronic nephritis. The features of this group of cases are progressive osteoporosis with or without fractures, unassociated with obvious dietary deficiencies, signs of chronic nephritis or hyperparathyroidism, in the presence of a normal serum calcium, low serum phosphorus, and increased phosphorus level and a decreased calcium excretion in the urine, often associated with renal glycosuria. The roentgen findings in the authors' case are illustrated.

Degenerative Bone Disease. Findings in 18 Cases with Posterior Spurs of the Lumbar Vertebrae. Walter M. Solomon. Am. J. M. Sc. **214:** 163–166, August 1947.

A survey of 629 lumbar spine examinations in patients complaining of low back pain showed spurs on the posterior aspects of the bodies in 18 cases. Signs of root irritation were found in 12 cases. The spurs are believed to develop as a result of degenerative changes in the intervertebral disks. As in the cervical spine, the spurs encroach on the intervertebral foramen and produce root symptoms.

BENJAMIN COPLEMAN, M.D.

The Disease Picture of Vertebra Plana Calvé as a Syndrome. Walter Hess. Schweiz. med. Wchnschr. **77:** 737–738, July 12, 1947.

The typical picture of vertebra plana as described by Calvé has hitherto been ascribed to aseptic necrosis, but the author briefly reports 2 cases in which a typical vertebra plana resulted from a pre-existing affection of the bone, in 1 case a von Recklinghausen's osteitis fibrosa and in the other a vertebral fracture due to tetanus. The conclusion is that vertebra plana is merely a syndrome without specific etiology or pathology, and aseptic necrosis can be diagnosed with certainty only if repair of the collapsed vertebra is observed.

LEWIS G. JACOBS, M.D.

Peripheral Extension of Radiopaque Media from the Subarachnoid Space. J. Douglas French and William H. Strain. Surgery **22:** 380–390, August 1947.

In 4 instances in a series of 200 consecutive myelograms, the injected pantopaque was seen to extend outside the normal confines of the subarachnoid space, apparently along the nerve roots. In one case the presence of diverticular extensions of the meninges was later proved at operation. In one other it was shown that the tip of the lumbar puncture needle had entered a nerve root. In a third case much of the pantopaque flowed readily out along several nerve roots, where it appeared to remain, although during a five-month follow-up the amount of medium diminished considerably.

Experimental studies on dogs and rabbits are reported in which it appears to be demonstrated that pantopaque extends out of the subarachnoid space only in the presence of a distinct anatomical abnormality or an injection irregularity. It is further indicated that the perineural spaces are merely connective-tissue planes in peripheral nerves which connect only indirectly with the subarachnoid space.

ALTON S. HANSEN, M.D.

Roentgen Evaluation of Lesions of the Carpus. F. F. Ruzicka and G. W. Heublein. Am. J. Roentgenol. **58:** 148–165, August 1947.

This paper discusses all types of lesions of the carpal bones and gives examples of most of them. The material was seen in a three-year period at Percy Jones General Hospital. All films were taken with a Morgan-Hodges phototimer and the authors recommend its use in all examinations of the carpus.

Of 16 fractures of the navicular taken without selection from the hospital files, 50 per cent occurred in the waist of the bone, 37.5 per cent in the proximal third, and the remainder in the distal third. The authors point out the variation in the blood supply of the navicular with frequent lack of nutrient arteries to the proximal portion. Poor mobilization with resultant destruction of the new blood-vessel-bearing granulation tissue is given as the cause of non-union and aseptic necrosis.

Fractures of the lunate are rare. Chip fractures of the dorsal tip are occasionally seen in association with dorsal perilunar dislocations. The authors believe that accessory ossicles about the lunate actually represent avulsion fractures. The more usual type of isolated lunate fracture is in the mid portion of the bone, from the concave to the convex surface. The deformity in such cases is best seen in the lateral projection. Three cases were encountered by the authors: one through the superior third of the bone, due to a gunshot wound; one through the center of the bone, with associated fractures of the triquetral and pisiform; and one chip fracture.

Three cases of dislocation of the lunate are illustrated, a simple volar dislocation, a perilunate dorsal dislocation, and an incomplete volar rotation.

Five cases of Kienböck's disease are included. The authors describe a dorsal tongue-like projection of the lunate over the head of the os magnum which they believe is strong evidence of Kienböck's disease.

Fractures of all the remaining carpal bones are described and illustrated. One example of aseptic necrosis of the head of the capitate without evidence of fracture was seen in a case of traumatic amputation at the carpal-metacarpal joint.

With the exception of the majority of the navicular fractures, most of the carpal fractures were multiple.

G. K. VOLLMAR, M.D.

THE GENITO-URINARY SYSTEM

Replacement Lipomatosis of the Kidney. Jacob Frumkin. J. Urol. **58:** 100–105, August 1947.

The replacement of renal parenchyma by fatty tissue occurs infrequently and has been reported in the literature under various descriptive titles, as fatty transformation of the kidney, lipomatosis renis, lipomatous nephritis, fatty degeneration of the kidney, *substitutio renis adiposa*, and others. In recent years the condition has been designated as fatty replacement or replacement lipomatosis. The author has briefly summarized the literature and presented an interesting case.

Normally the parenchyma of the kidney does not contain fat. The adipose tissue that is present in the

kidney is a continuation of the periureteral and perirenal fat which surrounds the pelvis and calices and lines the hilus, and through it course the main renal vessels. Consequently the appearance of fat in the medulla and cortex is to be regarded as a pathological condition.

Primary lipoma of the kidney is a relatively rare tumor, and when it occurs is surrounded by normal renal tissue. It should not be confused with replacement lipomatosis.

There are two principal theories concerning the etiology of replacement lipomatosis. According to one, chronic inflammatory processes stimulate an increase in the perirenal and peripelvic fat, which enters the kidney through the capsule or hilus, producing secondary atrophy of the kidney parenchyma. According to the other, the primary cause is atrophy of the renal parenchyma due to destructive processes, followed by fatty replacement arising from the normal peripelvic fat.

A review of the literature shows that fatty replacement generally occurs with kidney infection and, in the majority of cases, with calculous disease. A few cases have been reported following non-inflammatory lesions of the kidney, such as senile arteriosclerotic kidney, nephrosclerosis, amyloidosis, congenital hypoplasia, and chronic glomerulonephritis. The author feels that fatty lipomatosis is not as rare a condition as previously regarded, and that probably only the advanced cases have been reported.

Clinically, the diagnosis of fatty replacement has not been made prior to operation or autopsy. Symptoms vary according to the underlying pathological changes causing the destruction of renal tissue. Cystoscopy does not reveal any specific findings, though frequently a functionless kidney is discovered. Pyelography often shows a filling defect.

The features of the case reported by the author are in agreement with the salient facts as recorded in the literature. Diagnosis was made only after operation. The bulk of the kidney consisted of firm, fatty tissue through which ramified thick-walled calices in which calculi were present. The arterioles had thickened walls and small lumina. The renal units were reduced in number and replaced by inflammatory tissue. All the glomeruli exhibited sclerosis in varying degree, and most of them were completely fibrosed. The abundant fatty tissue was made up of normal fat cells, but there was considerable fibrous tissue in all portions.

JOHN W. HOPE, M.D.

Mullerian Duct Cyst. L. R. Culbertson. J. Urol. **58:** 134–136, August 1947.

In the male, abnormal remnants of the distal end of the fused müllerian ducts may undergo cystic dilation of variable degree. These cysts may communicate directly with the urethra through the utricle or may be connected only by a fibrous cord. Several previous reports are quoted, and the author expresses the opinion that the abnormality is more common than published accounts indicate.

Such a cyst was seen in a 33-year-old Croatan Indian, who gave a history of persistent burning and difficulty in starting the stream at urination, following an episode of sharp pain in both flanks, left lower quadrant, and testicle, upon lifting a heavy weight five months previously. He also felt a mass protruding from the rectum. Physical examination revealed tenderness in the left flank, incomplete atrophy of the left testis, and, arising from the base of the prostate, slightly to the right and not connected with it, a soft cystic mass. Cystourethroscopy showed the sinus pocularis to be quite prominent and a urethral catheter passed into the sinus permitted aspiration of 6 c.c. of thin milky fluid. The cyst was filled with sodium iodide and visualized radiographically.

A right seminal vesiculogram made by injecting the scrotal segment of the vas deferens with skiodan demonstrated displacement of the vesicle and ejaculatory ducts by the cyst.

The cyst was removed surgically through a perineal incision and symptoms subsided. Pathological examination revealed a lining of transitional epithelium inside a fibrous connective-tissue wall.

PAUL R. NOBLE, M.D.

Calcification of the Seminal Vesicles: Case Report. John D. Shea and Jack W. Schwartz. J. Urol. **58:** 132–133, August 1947.

The authors present a case of bilateral calcification of the seminal vesicles thought to have been of tuberculous origin. The function of the left upper urinary tract was apparently normal and there was no evidence of infection. The right kidney was non-functioning. On cystoscopic examination the catheter passed without obstruction to the left kidney pelvis. There was a complete obstruction to the ureteral catheter in the intramural portion of the right ureter. X-ray examination of the pelvis revealed two densely calcified shadows in the region of the base of the prostate. The right kidney was removed and found to be tuberculous and pyonephrotic. Following this operation, the patient made a slow but uneventful recovery and was discharged from the hospital with no complaints referable to the urinary tract.

The authors present a brief review of the literature. The condition is considered rare and only a few reports were to be found.

S. A. PATTERSON, M.D.

RADIOTHERAPY

Kaposi's Sarcoma or Lymphogranulomatosis Cutis. Report of a Case Treated with Roentgen Rays. Ernst A. Pohle and Elizabeth A. Clark. Urol. & Cutan. Rev. **51:** 382–385, July 1947.

Skin lesions of the lymphoblastoma group of diseases respond well to roentgen therapy, though the ultimate course of the disease is unaffected; new lesions appear as the old ones regress, and there is a tendency to the development of a relative radioresistance necessitating increasing dosage. In general, small doses are adequate to obtain regression of a given lesion (100 to 150 r on three successive days). These observations apply also to Kaposi's sarcoma.

The case recorded by the authors was notable for the widespread distribution of the cutaneous lesions and the excellent response to therapy. The original histologic diagnosis was Kaposi's sarcoma. Later a diagnosis of Hodgkin's disease was made. During two years and

nine months, a total of 26,958 r (in air) were given to 62 different lesions in 14 series of treatments, as well as one series of 100 r whole body irradiation. The patient maintained a good general condition for more than two years and was able to work full time for most of that period. Eventually adenopathy developed, the dermatitis progressed, and death ensued. Autopsy was not obtained. MAURICE D. SACHS, M.D.

Treatment of Melanosarcoma. Francesco Santagati. Radiol. med. (Milan). **33:** 337–350, July 1947.

The author reports on 38 cases of melanosarcoma treated at the Cancer Institute of Milan (Italy). Of these 38 cases, 14 were treated with contact roentgen therapy using a dosage of 10,000 to 15,000 r given over ten to twenty days. Three of the patients thus treated are well at the end of five years, 3 are well after three years, 3 are well after less than three years; 3 patients had recurrences and 2 did not report for examination.

Seven patients were treated with radium. Of these, 3 were well at the end of three years. Fourteen patients were treated surgically and following recurrences were given radium therapy. Of these, 6 were well after periods varying from one to three years. Three patients were treated with contact therapy following recurrence after surgery. Two of these patients have been well for six years.

The author concludes that radiation therapy, especially contact therapy, has a definite place in the treatment of melanosarcoma.

CESARE GIANTURCO, M.D.

Radium Therapy of Recurring Nasal Polyposis. J. Parkes Findlay. M. J. Australia **2:** 71–73, July 19, 1947.

The author presents a series of 40 cases of nasal polyposis treated by radium element or radon following surgical excision of the polyps. In 36 cases radium was inserted at the time of operation, without deleterious results; in the other 4 cases the interval between operation and radium application was from seven to twenty-eight days. No patients with infection were treated until the sinuses were clean, and most patients treated were without infection.

The radium applicator is introduced into position in the ethmoid cavity under the middle turbinate and is maintained *in situ* with bismuth paste gauze. A tube or container active at both ends is preferable, so that adequate radiation is delivered to anterior and posterior ethmoids and middle turbinate areas.

Twenty-eight patients were treated by radium element. Two tubes containing 25 mg. of radium element screened by 2.0 mm. of platinum were fitted into a rubber cot and packed in position for eight hours. The dosage was thus 200 mg. hours, resulting in a dose of 3,800 r at the surface and 1,050 r at a depth of 1 cm. in the plane of the tube.

Twelve patients were treated by radon. Two 25-mc. nasal applicators screened by 1.0 mm. of platinum were left *in situ* for seven hours, forty-nine minutes, giving a dose of 3,500 r at the surface.

Follow-up examinations are made at three months and one year following discharge of patients. Follow-up of the patients treated with radium element (1939–42) revealed four recurrences of a fibromyxomatous nature, which were readily removed. Of the patients treated by radon (1945–46), none had shown recurrences. SAVA M. ROBERTS, M.D.

Carcinoma of the Thyroid. Robert C. Horn, Jr., Robert F. Welty, Frank P. Brooks, Jonathan E. Rhoads, and Eugene P. Pendergrass. Ann. Surg. **126:** 140–155, August 1947.

The authors have reviewed 71 cases of carcinoma of the thyroid treated in the Hospital of the University of Pennsylvania since July 1933. Analysis of this series shows essential agreement with reports of other investigators. Thus, 70 per cent of cases occurred between the ages of forty-one and seventy; 76 per cent of the patients were females; 3 per cent showed unequivocal evidence of hyperthyroidism; a significant proportion of the carcinomas originated in nodular goiters. Metastases occurred in 25 of the 71 patients. The most frequent sites of involvement were the cervical lymph nodes, bones, and lungs.

Surgical removal is generally agreed to be the initial treatment of choice in thyroid cancer. In fact, the diagnosis is frequently unsuspected until after surgery has been performed. There is similar general agreement upon the efficacy of radiation therapy. One must be cautious, however, in speaking of "cures," since many patients remain well for five or more years following treatment, only to succumb later with extension of the malignant disease.

A majority of thyroid carcinomas are of the papillary or malignant adenoma type. Fifty-eight per cent of the patients treated for tumors of these types five years ago, and 60 per cent of those treated more than ten years ago, are alive and well.

So far as prognosis is concerned, the extent of the disease at the time treatment is instituted is more significant than the pathological type. Eighty-six per cent of the patients whose tumors were discovered only on pathological examination, and who were treated more than five years ago, are alive and well. Seventy-five per cent of such patients treated more than ten years ago are alive and well.

The authors recommend surgical excision of all nodular goiters in view of the relatively small risk of operation. If a carcinoma is present and extends through the capsule of the gland, postoperative irradiation should be instituted. It has been especially effective in the papillary carcinomas. The benefits of postoperative irradiation in cases in which the carcinoma has not extended through the capsule are not clear from the present study.

Most of the patients were given a total dose to the neck of about 5,000 r (air). Three portals were commonly used, two lateral and an anterior portal, with a posterior portal sometimes added. In order to permit physiological repair to occur, radiotherapy was not begun until at least two or three months following surgery. Irradiation was instituted immediately if the surgical procedure was limited to a simple exploration and biopsy. M. WENDELL DIETZ, M.D.

Bronchogenic Carcinoma—A Clinical-Pathological Study of 36 Autopsied Cases Seen at the Brooklyn Cancer Institute Between 1937 and 1945, Inclusive. William A. Henkin. Ann. Int. Med. **27:** 243–260, August 1947.

This report is based on the study of a series of 36 autopsied cases of bronchogenic carcinoma seen at the

Brooklyn Cancer Institute between 1937 and 1945.

The earliest and most common symptom, frequently overlooked for months, is a non-productive cough. The continuous trauma of coughing, together with degenerative changes in the tumor, leads to ulceration, with the production of blood-streaked or purulent sputum. Since most bronchogenic carcinomas originate in the major bronchi, positive diagnosis by bronchoscopic biopsy is often possible at this time. Physical examination and chest roentgenograms show no evidence of the disease in this stage.

As the growing tumor causes partial obstruction of the bronchus, the segment of lung distal to the affected bronchus becomes emphysematous. Wheezing or asthmatic breathing may appear. Usually this period of emphysema is of short duration and remains unrecognized while the enlarging tumor gradually produces complete bronchial obstruction and atelectasis. If the occluded bronchus is sufficiently large, a considerable shift of the mediastinum to the affected side occurs and a real decrease in functioning lung volume and dyspnea develop. Almost simultaneously secondary infection develops within the atelectatic segment as necrotic tumor tissue, mucus, pus, and bacteria accumulate. Leukocytosis, fever, and anemia appear at this time and persist virtually unalterable until death.

Tumor growth continues and leads to further bronchial obstruction with secondary infection. This cycle is responsible for the dangerous diagnosis of "recurrent pneumonia."

The earliest and most frequent pathologic change producing physical signs is atelectasis. Fluoroscopic findings, such as mediastinal shift to the atelectatic side on inspiration, elevation of the diaphragm, paradoxical elevation of the diaphragm on inspiration and narrowing of the intercostal spaces, are the result of atelectasis. The atelectatic area is manifest as a dense wedge-shaped shadow with relatively indefinite concave borders extending from the hilum toward the chest wall.

Not infrequently tumor cells reach the pleura, where they produce a reactive hemorrhagic pleural effusion. In time, sputum is aspirated into other bronchi producing numerous areas of bronchitis and pneumonitis.

In many cases the tumor develops so insidiously that the presenting signs and symptoms are those of distant metastasis or local mediastinal extension. In the present series cerebral metastases were found at autopsy in 7 cases. In 2 of these cases the initial symptoms, headaches and convulsions in one and gradual hemiparesis in the other, pointed to a primary brain tumor. Roentgenographic study of the chest revealed the true primary site in both cases.

Bone metastases were found in 19 patients (53 per cent) during antemortem roentgen examinations. The findings were corroborated in 14 (40 per cent) of these patients at necropsy.

In the last analysis the diagnosis of bronchogenic carcinoma can be established only by the microscopic examination of an adequate biopsy specimen. In early cases the specimen is obtained either at bronchoscopy or at thoracotomy. In later stages subcutaneous nodules or involved lymph nodes can be biopsied. Pleural fluid may contain cells whose appearance is suggestive of a malignant lesion. Sputum rarely shows malignant cells when studied by the older technics. Aspiration of bronchial secretions at bronchoscopy and staining by Papanicolaou's method should be performed more often.

Bronchogenic carcinoma spreads by direct extension, by extension to regional lymph nodes along peribronchial and perivascular lymphatics, and by vascular invasion. Rarely growth along the bronchial mucosa is seen.

Bronchogenic carcinoma runs a rapid course. No patient in the series reported lived longer than 28 months after the appearance of symptoms. If the disease is not curable surgically by pneumonectomy, it is not curable. Roentgen therapy should be given for its palliative effect as soon as possible after resectability has been found to be impossible, though in some cases no improvement will be obtained.

In this small series there were 11 patients who lived fifteen or more months after the onset of symptoms. In this group there was no relation whatever between the tumor dose administered and longevity. Three of these patients received tumor doses of 3,600 r or more. Two showed marked clearing of atelectasis; one showed no roentgen changes but gained weight and manifested considerable clinical improvement. In 4 cases, tumor doses of 3,000, 3,300, 4,000, and 3,800 r were given with survivals of only six, six, eight, and eight months, respectively. Only the fourth of these cases showed any effect of radiation that could be measured objectively—complete disappearance of the primary tumor.

STEPHEN N. TAGER, M.D.

Advances in Practical Prevention of Gynecologic Cancer. Robert J. Crossen. Am. J. Obst. & Gynec. **54:** 179–187, August 1947.

Prevention of gynecologic cancer involves the removal of chronic irritation, by conization for cervicitis and by vulvectomy for leukoplakic vulvitis, and the removal of involuting ovaries and uterus under suitable circumstances.

Periodic examinations are necessary to discover chronic irritation before malignant development starts and to discover cancer in involuting ovaries or uterus or breasts while it is still in a curable stage. Yearly check-ups were formerly considered sufficient, but owing to the difficulties of detecting early ovarian cancer that interval is believed to be too long. That fact was learned by bitter experience. A patient whose adnexal areas were apparently clear on examination returned seven months later with an irremovable ovarian cancer. Careful check-ups at six-month intervals for the two decades, forty to sixty years, constitute the minimum requirement for reasonable safety from incurable cancer. The cancer-potential of the involuting endometrium should be taken into consideration when handling non-malignant uterine conditions requiring serious treatment. For example, a myoma causing persistent grave symptoms in spite of palliative measures confronts us with the alternative of stopping the myoma activity by radium treatment (with curettage to exclude malignancy and conization if cervicitis is present) or removing the growth by the major operation of hysterectomy.

This calls for careful consideration of three factors, namely, (*a*) the chance, in the particular case, of securing relief by irradiation; (*b*) the future risk of malignant development in uterus or ovaries; (*c*) the immediate risk of hysterectomy and double oophorectomy. In a series of 500 myoma-radiation cases, it was found that though the risk of future malignant development was cut to one-third by radium treatment, there still remained

a risk of 0.89 per cent. The mortality risk of hysterectomy and double oophorectomy may be reckoned at 1 to 2 per cent, depending on the condition of the patient and the skill of the operator. Giving proper weight to these various factors in the study of the individual case will insure the safest and best treatment.

In general, for the good operative risk, the seriously troublesome myoma occurring in the age of involution is preferably handled by complete hysterectomy and double oophorectomy. On the other hand, for the seriously handicapped patient, radium therapy in a suitable case is a life-saving measure, in that it stops the serious myoma activity without the great risk of a major operation. Leukoplakic vulvitis eventuates in cancer in a considerable proportion of cases. Hence, the importance of prompt vulvectomy for this condition, unless there is a good response to vitamin A therapy as suggested by Hyams and Bloom (Am. J. Obst. & Gynec. **53:** 214, 1947).

A delayed menopause indicates erratic endometrial and ovarian activity which increases the susceptibility to malignant development. Menstrual activity should be stopped by radium treatment, with associated curettage to exclude endometrial cancer, conization if cervicitis is present, and accurate palpation of the ovarian areas under anesthesia, with recording of findings for future reference and comparison.

HUGH A. O'NEILL, M.D.

Common Peculiarities of Patients with Adenocarcinoma of the Endometrium, with Special Reference to Obesity, Body Build, Diabetes and Hypertension. William T. Moss. Am. J. Roentgenol. **58:** 203–210, August 1947.

The author reviews the literature as regards the physical characteristics of patients with adenocarcinoma of the endometrium and reports a series of 23 cases. It is noted that a large percentage of these patients were obese and that a combination of obesity and lateral body build was present in 61 per cent of the group. Fifteen patients had abnormal glucose tolerance curves; 18 had abnormally high blood pressure. All of these findings were of higher incidence than in average groups of comparable age. It follows that post-menopausal bleeding in the obese, hypertensive patient who has a diabetic tendency should be studied with special care.

Body build was believed to be the most important single factor in the series studied. This does not imply that the lateral type of build produces cancer of the endometrium but that perhaps the same factor or factors may play a role in both states in the same individual.

G. K. VOLLMAR, M.D.

Effect of Grenz Rays on Leprous Infiltrations. III. Response of Lesions of the Anterior Portions of the Eyeball. F. Sagher and B. Miterstein. Arch. Ophthmal. **38:** 78–88, July 1947.

Grenz rays were applied to lepromatous changes in the anterior segments of the eyeball in 6 patients. Rays of various grades of "hardness" were employed, the voltage ranging from 6 to 14 kv., which is equivalent to half-value layers of 0.021 to 0.031 of aluminum. The most effective doses applied at one sitting were from 700 to 1,200 r, with total dosage varying from 5,500 to 11,600 r. These larges doses could be applied safely to the external tissues of the eye because the sensitivity of such tissues to irradiation is lower than that of the skin. In 3 patients with practically sightless eyes the lepromas undoubtedly were reduced in size or disappeared completely. Of 3 patients with fairly good vision, 2 showed a favorable response; in the third the irradiated lepromatous part became quiescent or even slightly flatter, while the surrounding parts presented rapid growth of new lepromas. No damage to the cornea, lens, or deeper structures of the eye was observed, so far as could be determined by a follow-up of two to four years.

Peyronie's Disease or Plastic Induration of the Penis. Roy C. Giles. Urol. & Cutan. Rev. **51:** 399–400, July 1947.

Roentgen therapy is recommended for the treatment of Peyronie's disease, or plastic induration of the penis, but the 3 cases reported show diverse results. The first patient, who consulted a physician six to eight months after discovery of the induration, responded well to treatment (10 weekly treatments of 200 r each; 200 kv., 50 cm. distance, 0.5 mm. Cu filter, and a portal just covering the area involved). In the second case, therapy (same factors) was instituted six years after onset of the disease but only slight improvement was obtained. The third case was of three years' duration and was treated by surgical intervention with postoperative roentgen irradiation, but the results were poor.

MAURICE D. SACHS, M.D.

Care of the Patient Who Has Myasthenia Gravis. L. M. Eaton. M. Clin. North America **31:** 907–923, July 1947.

The author considers all phases of the treatment of myasthenia gravis, but only that part of the discussion dealing with radiotherapy will be abstracted here. The value of roentgen irradiation of the thymus is difficult to determine. A study of 100 consecutive patients thus treated revealed that only 18 per cent experienced a remission during the ensuing twelve months. The amount of roentgen therapy administered is believed, however, to have been grossly insufficient. Roentgen irradiation is often advised when a patient is too ill to withstand operation. The thymic area is irradiated through two anterior and two posterior fields cross-firing at the anterior mediastinum from the level of the cricoid cartilage to the diaphragm. The technical factors usually are 130 kv., 6 ma., 5 mm. aluminum filter, distance 40 cm.; time, eight to fifteen minutes per field, with a dose of 32 r per minute. When a mediastinal tumor is present, the time averages sixteen minutes per field. The treatments are given on successive days and the series is repeated in one to two months. The total dose is not stated.

Radiophosphorus in the Treatment of Blood Dyscrasias. Byron E. Hall and Charles H. Watkins. M. Clin. North America **31:** 810–840, July 1947.

Since the fall of 1941, 143 patients with diseases involving primarily the bone marrow have been treated at the Mayo Clinic. This number includes 97 cases of polycythemia vera; 22 of myeloma; 17 of myelogenous leukemia; 3 of chronic lymphatic leukemia; 2 of monocytic leukemia, and 2 of Hodgkin's disease of the bone marrow.

Radiophosphorus was found to be most effective in polycythemia vera. While in no way curative, it resulted in the induction of remissions in a high proportion

of cases. Fifty-four of the 97 patients with polycythemia have been followed from nine months to four and a half years. The other 43 patients were treated during the nine months prior to the preparation of this paper and data concerning them are not included. In 32 cases, the diagnosis had been made months or years previously and the patient had been treated by other means. In only 2 of these was the polycythemia under adequate control when the patient was admitted for treatment with radiophosphorus. The most striking improvement following the administration of radiophosphorus was in the group of symptoms attributable to increased blood volume; namely, headache, sense of fullness or pressure in the head, dizziness, and visual disturbances. Fatigue was a common symptom and was relieved completely in 24 cases. In 30 patients with splenomegaly on whom follow-up data were available, the spleen was reduced in size in 27. In 11 of 12 patients with hepatomegaly, on whom follow-up data are adequate, a reduction in size of the liver was noted. Some degree of improvement in the hematologic picture was noted in all cases in which radiophosphorus was used. In individuals whose erythrocytes numbered in the neighborhood of 6,000,000 cells per cubic millimeter, not infrequently a normal cell volume was obtained. Patients whose cell volume per cent fell to less than 55 and whose erythrocytes decreased in number to less than 5,500,000 per cubic millimeter were found to be relieved of those symptoms generally attributed to increased blood volume, whereas patients in whom a fall in cell volume per cent and number of erythrocytes per cubic millimeter was not sufficient to give values of less than 55 for packed cells and 5,500,000 for erythrocytes, obtained partial but not complete relief of similar symptoms.

Fifteen of the 54 patients have had two courses of treatment with radiophosphorus, and 6 of the 15 have had three courses of treatment. Fifty-one of the 54 patients are living. The complications encountered with this form of treatment are largely hematologic, in the form of thrombocytopenia, leukopenia, and anemia.

In the chronic types of leukemia, treatment with radiophosphorus induced remissions similar to those induced by roentgen therapy, but it had no particular advantage over that form of treatment and required a longer period of time to bring about the desired result. However, once a remission had been induced by roentgen irradiation, radiophosphorus was found to be effective in holding leukocyte counts near normal for long periods of time.

Radiophosphorus was ineffectual in inhibiting the progression of acute leukemia, Hodgkin's disease, and multiple myeloma. In more than 50 per cent of the cases of myeloma, it afforded varying degrees of relief from pain in the bones.

RADIATION EFFECTS

The Medical Sequelae of the Atomic Bomb Explosion. George V. LeRoy. J. A. M. A. **134:** 1143–1148, Aug. 2, 1947.

The two major phenomena due to the atomic bomb explosion which endangered life were the gastrointestinal disturbances and the destruction of the hematopoietic tissues. Many patients undoubtedly died from dehydration and acidosis resulting from the intense diarrhea and vomiting and the ulceration that occurred throughout the bowel. The damage to the bone marrow was even more serious, although it appears from histologic studies that regeneration of a sort commenced soon after injury. Severe leukopenia, which persisted for a period of one to three weeks, facilitated the development of overwhelming infections in any part of the body. The hemorrhagic state accompanying the thrombocytopenia was capable of causing exsanguination from ulcerating mucous membranes or from wounds, as well as fatal hemorrhages in the central nervous system, the myocardium, or the adrenal glands.

Therapy in patients exposed to the amount of gamma radiation emitted by an exploding atomic bomb should be directed toward the maintenance of fluid and acid-base balance, control of infectious processes, combating the hemorrhagic tendency, and correction of the anemia.

Gross Autopsy Observations in the Animals Exposed at Bikini. A Preliminary Report. John L. Tullis and Shields Warren. J. A. M. A. **134:** 1155–1158, Aug. 2, 1947.

From observation of animals exposed at Bikini, several conclusions seem justified:

1. Ionizing radiations of the atomic bomb are lethal for goats, pigs, guniea-pigs, and rats exposed to them under varying conditions.

2. The gross pathologic observations are fairly characteristic and similar in the four species studied.

3. The sensitivity to ionizing radiations varies somewhat among the four species, the guinea-pigs being by far the most sensitive, the pigs being slightly more sensitive than the goats, and the rats comparatively resistant.

4. The flimsiest of shielding seems to afford ample protection from thermal radiation, but heavy armor does not always protect from the ionizing radiations.

5. An underwater atomic bomb explosion is more lethal than an air explosion, since the spray which showers down on the ships in the vicinity carries with it contaminating fission products which cannot be removed easily and remain dangerously radioactive for long periods of time.

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